CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-641

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Pharmacology/Toxicology Data
NDA 21-641

Drug:	Azilect (Rasagiline Mesylate) Tablet
Submission:	Class I Resubmission-Complete Response
Submitted:	March 17, 2006
Reviewed:	May 4, 2006
Reviewer:	Paul Roney
Drug Class:	Dopamine Agonist
Indication:	Parkinson's Disease
Sponsor:	Teva Neuroscience

The Sponsor has submitted a complete response to the Divisions Approvable Letter of August 4, 2005. There were no pre-Approval non-clinical issues in the Approvable letter. There was one post-Approval non-clinical issue, the Sponsor needed to conduct an embryo-fetal development study in rabbits. In this submission, the Sponsor states that they have completed the in-life portion of this study and anticipates submitting the study in October 2006.

The sponsor has proposed changes to labeling. The changes with respect to nonclinical data were restricted to the Carcinogenesis, Mutagenesis, Impairment of Fertility section. Text the sponsor added is underlined in red; text the sponsor deleted is in ~~strikethrough in red~~. After each paragraph, this reviewer's comments on the proposed changes are in *italics*.

Page 2 of annotated label
Mechanisms of Action

The relevance of the — *is uncertain. This statement should be removed from the label.*

Pages 18-20 of annotated label
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis:
Two year carcinogenicity studies were conducted in CD-1 mice at oral (gavage) doses of 1, 15, and 45 mg/kg and in Sprague-Dawley rats at oral (gavage) doses of 0.3, 1, and 3 mg/kg (males) or 0.5, 2, 5, and 17 mg/kg (females). In rats, there was no increase in tumors.

In this paragraph, the Sponsor describes the results of the full rat carcinogenicity study. The description is acceptable except that the plasma ratios should be 33 for males at 3 mg/kg and 260 for females at 17 mg/kg.

In mice, there was an increase in lung tumors (combined adenomas/carcinomas) at 15 and 45 mg/kg males and females.

Plasma exposures associated with the no-effect dose (1 mg/kg) were approximately 5 times those expected in humans.

The sponsor's proposed language does not add to the clarity of this section. It is recommended that the original language be retained.

The carcinogenic potential of rasagiline administered in combination with levodopa/carbidopa has not been examined.

Mutagenesis:

Rasagiline was ~~reproducibly~~ clastogenic in *in vitro* chromosomal aberration assays in human lymphocytes in the presence of metabolic activation only and ~~was mutagenic and clastogenic~~ in the *in vitro* mouse lymphoma tk assay in the ~~absence and~~ presence of metabolic activation. Rasagiline was negative in the *in vitro* bacterial reverse mutation (Ames) assay), the *in vivo* unscheduled DNA synthesis assay, and the *in vivo* micronucleus assay in CD-1 mice. Rasagiline was also negative in the *in vivo* micronucleus assay in CD-1 mice when administered in combination with levodopa/carbidopa.

In this paragraph, the sponsor suggests that rasagiline was negative in the mouse lymphoma assay in the absence of metabolic activation. The sponsor points out that rasagiline was positive only at the highest dose tested. The sponsor argues that the rasagiline was "highly cytotoxic and relative growth was inhibited by about 80%" (page 1 of label_clarifications.pdf). The highest dose did reduce growth by 79.8% (relative growth was 20.2% of control). However, ICH guidance S2A (Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals) states that "In mammalian cell mutation tests, ideally the highest concentration should produce at least 80 percent toxicity (no more than 20 percent survival)" (page 3 of guidance). In addition, the guidance states "Caution is due with positive results obtained at levels of survival lower than 10 percent." (page 3 of guidance). Thus, the results of this assay are within ICH Guidance for a valid test. The sponsor also argues that rasagiline just exceeded the minimum criteria for a positive test (125.6 mutations/million cells versus a threshold of 120.5 mutations/million cells). Nevertheless, the incidence was above the threshold and the test must be considered positive. The other sponsor edits do not add to the clarity of the paragraph. It is recommended that the original FDA language be retained.

Impairment of Fertility:

Rasagiline had no effect on mating performance or fertility in male rats treated prior to and throughout the mating period, or in female rats treated from prior to mating through day 17 of gestation at oral doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [1 mg/day]). The effect of rasagiline administered in combination with levodopa/carbidopa on mating and fertility has not been examined.

Pregnancy Category C

No effect on embryo-fetal development was observed in a combined mating/fertility and embryo-fetal development study in female rats at doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [MRHD, 1 mg/day]). ~~Effects on embryo-fetal development in rabbit have not been adequately assessed.~~

The sponsor contends that the effects of rasagiline on embryo-fetal development have been adequately addressed. As noted in a previous review by this reviewer (dated July 14,2005, Submission dated November 4, 2004), this is not the case. The original FDA language should be retained.

In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) orally, from the beginning of organogenesis to day 20 post-partum, offspring survival was decreased and offspring body weight was reduced at doses of 0.3 mg/kg/day and 1 mg/kg/day (10 and 16 times the expected plasma rasagiline exposure [AUC] at the MRHD). No plasma data were available at the no-effect dose (0.1 mg/kg); however, that dose is 1 times the MRHD on a mg/m^2 basis. ~~Rasagiline's effect on physical and behavioral development was not adequately assessed in this study.~~

In this paragraph, the sponsor is removing language concerning the inadequate assessment of physical and behavioral development in the Segment 3 reproductive toxicity study. The original language should be retained.

Rasagiline may be given as an adjunct therapy to levodopa/carbidopa treatment. In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day) (alone and in combination) throughout the period of organogenesis, there was an increased incidence of wavy ribs in fetuses from rats treated with rasagiline in combination with levodopa/carbidopa at 1/80/20 mg/kg/day (approximately 8 times the plasma AUC expected in humans at the MRHD and 1/1 times the MRHD of levodopa/carbidopa [800 – 200 mg/day] on a mg/m^2 basis). In a study in which pregnant rabbits were dosed throughout the period of organogenesis with rasagiline alone (3 mg/kg) or in combination with levodopa/carbidopa (rasagiline: 0.1, 0.6, 1.2 mg/kg, levodopa/carbidopa: 80/20 mg/kg/day), an increase in embryo-fetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day when administered in combination with levodopa/carbidopa (approximately 7 and 13 times, respectively, the plasma rasagiline AUC at the MRHD). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone (~~0.~~1/1 times the MRHD on a mg/m^2 basis) and to a greater extent when rasagiline (at all doses; 1-13 times the plasma rasagiline AUC at the MRHD) was administered in combination with levodopa/carbidopa.

In this paragraph, the sponsor corrects some errors with regards to the clinical Sinemet dose and ratio to human dose. This is acceptable. The sponsor also adds language

s. This statement is not sufficiently supported by the data. It should be deleted.

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/s/

Paul Roney
5/4/2006 02:30:35 PM
PHARMACOLOGIST

Lois Freed
5/4/2006 06:23:14 PM
PHARMACOLOGIST
I concur with the labeling recommendations.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 8/3/05

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-641 (rasagiline mesylate, AGILECT™)

The nonclinical data in the sponsor's response to the Agency's Approvable letter (issued July 2, 2004) has been reviewed by Paul Roney, Ph.D. (Pharmacology/Toxicology Review and Evaluation, NDA 21-641, 7/14/05). The sponsor was asked to address three nonclinical issues: (1) the need for further evaluation of tissues from the 2-year carcinogenicity study in rats, (2) the potential for genotoxic impurities to arise during synthesis of the drug substance, and (3) the need to repeat the oral embryo-fetal development study in rabbits — Project No. 671411). Each issue is discussed below:

1. Dr. Roney concluded that the sponsor has adequately addressed the need for further evaluation of tissues from the 2-year carcinogenicity study in Sprague-Dawley rats. In the sponsor's original evaluation, tissues from only the control and high-dose groups (male and female) were examined microscopically. Due to the excessive body weight effects (>10% decrease compared to controls) observed at the high dose in both males and females, there was concern that the high dose may not have adequately characterized the potential tumorigenic risk of rasagiline. The sponsor was asked to conduct a microscopic examination of all tissues from the low and mid-dose groups for both males and females. Those data were submitted, although there were substantial problems with the electronic datasets submitted for FDA's statistical evaluation (documented in Dr. Tristan Massie's statistical review and evaluation, 7/20/05).

According to Dr. Massie's original statistical evaluation (based on analysis of tissues primarily from control and high-dose animals), there were no significant tumor findings in rats. The only new observation resulting from the analysis of tumor data from all dose groups was a statistically significant positive trend for benign granulosa/theca cell tumors of the ovary (0, 0, 0, 0, 1, and 2 at 0, 0, 0.5, 2, 5, and 17 mg/kg, respectively). However, the trend test was not statistically significant if the high-dose data were omitted, and pair-wise comparison of the control and high-dose groups was not statistically significant. Ovarian granulosa/theca cell tumors are rare in rats, so that not achieving statistical significant may not necessarily suggest the lack of tumorigenic risk. However, a Sertoli cell tumor (malignant; also rare) was detected in 1 control female. Since granulosa/theca and Sertoli cell tumors belong to the same major category of neoplasms of the ovary (i.e., gonadal stromal neoplasms) (Carlton WW *Neoplasms of Rodents*. 41st annual meeting. Pathology of Laboratory Animals, Uniformed Services University, August 1994), they may be combined (McConnell EE et al *J Natl Cancer Inst* 76(2):283-289, 1986). The incidences of the

combined tumors would then be 0, 1, 0, 1, and 2 (non-significant by trend test). (One additional ovarian tumor (a benign interstitial adenoma) was detected in a control female; this tumor type (an epithelial neoplasm, also rare in rats) may not be combined with the granulosa/theca and Sertoli cell tumors.) Therefore, there are no significant tumor findings in rats.

However, as Dr. Roney notes, one finding of concern is the malignant melanoma of the pinna detected in 1 HDM rat (1 of 130 total high-dose animals) (cf. conclusions at the end of this section for discussion of a finding in 1 control animal). The concern is primarily based on the possibility of a signal for melanoma in the clinical trials database. It is difficult to interpret the finding of a single incidence of a rare tumor type in a 2-year carcinogenicity study. It is not surprising that melanomas (neoplasms of melanogenic cells) are rare in albino animals. However, Greaves (In: Greaves P. *Histopathology of preclinical toxicity studies.* 2nd ed. Elsevier, Amsterdam, 2000, pg 25-26.) notes that

> "Over recent years amelanotic melanoma has been increasingly recognized in rats. In F-334/N rats they occur in less than 1% of aged animals and the pinna is a frequent site. They show the cellular features of melanoma but are devoid of pigment...electron microscopy shows intracytoplasmic premelanosomes, single membrane bound organelles containing membranous filaments..."

Greaves (2000) cites two published studies (Yoshitomi K et al. *Toxicol Path* 23(1):16-25, 1995, Nakashima N et al. *Toxicol Path* 24(2):158-261, 1996). According to the abstract, Yoshitomi et al. (1995) reported spontaneous incidence rates for amelanotic melanomas of the skin in Fisher 344 rats (70/11,171 males and 51/10,927 females) in 63 2-year carcinogenicity studies conducted by the NCI. Of the total of 121 melanomas, the majority occurred in the pinna (84), with lesser incidence in eyelid (19), scrotum (10), and perianal region (8). Interestingly, Yoshitomi et al (1995) reported that only the tumors of the pinna were metastatic. Earlier publications by Yoshitomi and Boorman (Yoshitomi K, Boorman GA *Vet Pathol* 28(5):403-409, 1991; Yoshitomi K, Boorman GA *Vet Pathol* 30(3):280-286, 1993) reported spontaneous amelanotic melanomas of the uveal tract and eyelids of F344 rats. According to the abstract, five intraocular melanomas were detected in "records from more than 60,000 females and 60,000 male F344 rats, which were used as control and treated animals in 2-year carcinogenicity studies" (Yoshitomi & Boorman, 1991). According to the abstract, spontaneous amelanotic melanomas were detected in the eyelids of 1/926 (0.11%) male and 5/925 (0.54%) female F344 rats "that were used as control and treated animals in five different carcinogenicity studies..." conducted by NTP. Nakashima et al (1996) reported a spontaneous amelanotic melanoma in the pinna of one F344 rat; the total number of animals was not specified in the abstract. In an earlier publication, Nakashima et al (Nakashima N et al. *J Vet Med Sci* 53(2):291-296, 1991) reported spontaneous amelanotic melanocytic tumors in 6/1920 male and female F344 rats from 3 24-month carcinogenicity studies. According to the 2001 Charles River spontaneous tumor incidence rates in Sprague-Dawley rats (the strain used in the rasagiline carcinogenicity study), benign amelanotic melanoma of the eye was detected in 1/1531 males and 1/1729 females; in addition, a malignant melanoma was detected in the pinna of 1/1531 males (none reported in 1729 females). It is unclear whether the melanomas in the eye and pinna in males were detected in the same or different animals. In the one published study in Sprague-Dawley rats (Zwicker GM et al *Toxicol Path* 20(3)(Part 1): 327-340, 1992), malignant melanoma of the skin (location not specified) was detected in 1/717 (0.1%) males and 1/716 (0.1%) females; according to the authors, there had been no previously published reports of spontaneous skin epithelial and mesenchymal neoplasms in Sprague-Dawley rats.

These reports indicate that melanomas do occur spontaneously in albino animals, albeit at a very low incidence (≤0.6%). (The incidence in high-dose rats in the rasagiline carcinogenicity study was 1/130 or 0.8%.) Although there have also been reports of compound-induced melanomas in albino animals (e.g., Albert DM et al. *Invest Ophthalmol Vis Sci* 22(6):768-782, 1982; Gomez S et al. *Pigment Cell Res* 1(6):390-396, 1988), one might assume that albino animals are relatively insensitive to treatment-induced melanomas compared to pigmented animals. Since both 2-year carcinogenicity studies of rasagiline were conducted in albino animals, it is unlikely that the potential for rasagiline to specifically induce melanomas has been adequately assessed in animals.

In mice, rasagiline induced lung tumors in both males and females (discussed in detail in Dr. Roney's reviews, 6/25/04 and 7/14/05). The incidences of alveolar bronchiolar adenomas and carcinomas are summarized in the following table (doses in mg/kg):

FINDING	MALE				FEMALE			
	0*	1	15	45	0*	1	15	45
adenoma	10/55	6/55	17/55	13/55	12/55	8/55	11/55	17/55
carcinoma	6/55	6/55	9/55	13/55	2/55	5/55	8/55	5/55

*control incidences were consistent with historical control data

According to FDA's independent statistical evaluation (Tristan Massie, Ph.D. 2/2/04), trend tests for adenomas or carcinomas alone were not statistically significant in either males or females. The trend test on combined adenomas/carcinomas was statistically significant in males, but not in females. Pairwise comparisons indicated a statistically significant increase in alveolar bronchiolar adenomas and combined adenomas/carcinomas in high-dose males. Dr. Roney notes that although not statistically significant, increases at the mid-dose in males and at the mid- and high-doses in females should be considered biologically significant considering the significant effect in high-dose males. As Dr. Roney also notes, plasma rasagiline exposure (AUC) in females was substantially lower than in males; at the high dose, the AUC in females was almost 3-fold lower than in males. (Plasma AUCs at the mid-dose were fairly similar in males and females; plasma AUCs for the metabolite, AI, were fairly similar in males and females at all doses.) Also, the data suggest that an MTD was not achieved in females. Therefore, there may have been reduced assay sensitivity in females (at least at the high dose), and the increases in lung tumors in females cannot be dismissed even though they did not achieve statistical significance. (According to the sponsor, there was also a significant increase in Harderian gland tumors in mice; however, according to FDA's independent statistical analysis, the increases in this tumor type (combined adenomas/carcinomas) were not statistically significant by trend test.)

Therefore, the one significant tumor finding was in lung, a common tumor site in mice (as evidenced by the incidence rates in the control groups in the 2-year study). Rasagiline did not induced a rare tumor, induce tumors at multiple sites, or tumors in both animal species, all characteristics thought to indicate higher predictive value for carcinogenic risk (Gray GM et al. *Reg Toxicol Pharmacol* 22:283-291, 1995). However, rasagiline did increase lung tumors in both males and females in one species and in a dose-related manner, which increases the concern for carcinogenic potential. The tumor findings are not entirely consistent with either a genotoxic or nongenotoxic mechanism. Nongenotoxic carcinogens tend to induce tumors only at high doses, in only one sex, or in only one animal species. Genotoxic carcinogens tend to induced tumors at multiple sites and/or in more than one animal species. Since rasagiline was positive (with and without metabolic activation, depending upon the assay) in in vitro studies in human peripheral lymphocytes and in the in vitro mouse lymphoma assay, a genotoxic mechanism cannot be ruled out (cf. Dr. Roney's review, 6/25/04, for a detailed discussion). The sponsor has conducted no studies to further evaluate the potential mechanism(s) underlying the lung tumors; for example,

reversibility, noted to be a "common characteristic" of nongenotoxic carcinogens (Lima BS, Van der Laan JW *Reg Toxicol Pharmacol* 32:135-143, 2000, was not assessed.

Another important consideration is how rasagiline's genotoxic and carcinogenic potential compares to approved therapies for Parkinson's disease with relevant nonclinical data. However, it is acknowledged that meaningful comparisons are difficult given the differences among studies in a number of factors, e.g., strain, route/method of dosing, changes in spontaneous tumor incidence over time, diet, adequacy of dosing. The following information is taken from the PDR except as noted:

1. Entacapone (COMTAN®), a reversible inhibitor of catechol-O-methyltransferase (COMT), increased both small and large colonies (i.e., both mutagenic and clastogenic) in the in vitro mouse lymphoma tk assay, and was positive in the in vitro chromosomal aberration assay in human peripheral lymphocytes. In the 2-year carcinogenicity study in rat, entacapone increased the incidence of renal tubular adenomas and carcinomas in males (at the high-dose). Entacapone was negative in the 2-year carcinogenicity study in mouse; however, high mortality at the high dose precluded an adequate assessment of carcinogenic potential.

2. Pramipexole (MIRAPEX®), a dopamine receptor agonist, was negative in the standard genotoxicity battery, and in 2-year carcinogenicity studies in mice and rats.

3. Tolcapone (TASMAR®), a reversible inhibitor of COMT, was positive (clastogenic) in the in vitro mouse lymphoma tk assay in the presence of metabolic activation, and negative in the rest of the standard genotoxicity battery. Tolcapone was also negative in a 80-95 wk carcinogenicity study in mouse. In the 2-year carcinogenicity in rats, tolcapone was associated with an increase in uterine adenocarcinomas, "A low incidence of renal tubular cell adenomas...in middle- and high-dose female rats; tubular cell carcinomas occurred in middle- and high-dose male and high-dose female rats..."; the increase was statistically significant in high-dose males.

4. Ropinirole (REQUIP®), a dopamine receptor agonist, was negative in the standard genotoxicity battery. In the 2-year carcinogenicity in rat, there was an increase in testicular Leydig cell adenomas, a tumor type considered irrelevant to humans. In the 2-year carcinogenicity study in mouse, there was an increase in benign uterine endometrial polyps at 10 times the maximum recommended human dose (mg/m^2).

5. Pergolide (PERMAX®), a dopamine receptor agonist, exhibited a "weak mutagenic response...in the mammalian cell-point-mutation assay only after metabolic activation with rat liver microsomes"; pergolide was negative in the other genotoxicity assays (i.e., in vitro Ames assay, in vivo micronucleus assay). In the 2-year carcinogenicity studies in mouse and rat, there was "A low incidence of uterine neoplasms... in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice." These tumors were thought to result from endocrine effects not present in humans.

6. Labeling for selegiline (ELDEPRYL®), an irreversible inhibitor of MAO-B (as is rasagiline), has not been updated in the most recent PDR. However, according to the labeling sent to the sponsor in the Approvable letter for EMSAM (NDA 21-336, 21-708), selegiline was positive in the in vitro mouse lymphoma tk assay in the absence and presence of metabolic activation, but was negative in the rest of the standard genotoxicity

battery. No tumor findings were observed in a 2-year carcinogenicity study in rat; however, substantial body weight effects may have reduced the sensitivity to detect carcinogenic potential. (A 78-week carcinogenicity study in mouse was also negative, but considered inadequate for similar reasons.)

In comparing the reported genotoxicity and carcinogenicity findings for these approved therapies (with the caveats noted), it would appear that findings with two drugs, entacapone and tolcapone, are somewhat comparable to those with rasagiline. Selegiline, an irreversible MAO-B inhibitor (as is rasagiline), was positive in an in vitro genotoxicity assay, but negative in carcinogenicity studies (although body weight effects may have reduced the sensitivity of these studies).

Conclusion: Taken together, I believe the data for rasagiline indicate a potential carcinogenic risk to humans, possibly via a genotoxic mechanism. This conclusion is based on the lung tumor findings in mice and the positive (although not entirely consistent) findings in the in vitro mammalian cell genotoxicity assays.

There appears to be a concern that rasagiline may increase the incidence of melanoma in humans, based on the clinical trials database. There was a single occurrence of malignant melanoma in high-dose male in the 2-year rat carcinogenicity study. However, it is impossible to conclude that this one occurrence in animals strengthens the clinical concern. Although rare (<1%), melanomas do occur spontaneously in albino animals, as noted in a number of published studies (primarily in F344 rats). What does cause concern regarding this tumor type is that both 2-year carcinogenicity studies were conducted in albino animals (Sprague-Dawley rat, CD-1 mouse). Assuming that albino animals (lacking melanocytes) are insensitive models for assessing the risk of treatment-induced melanomas, the potential for rasagiline to induce this tumor type has not been adequately assessed.

The nonclinical genotoxicity and carcinogenicity findings are somewhat similar to some drugs approved for PD. However, a potential signal for carcinogenicity in humans would greatly increase concern for rasagiline, particularly considering the unlikelihood of detecting such a signal during clinical development. If it is concluded that there is a potential clinical signal for melanoma, then it is recommended that the sponsor conduct additional studies in pigmented animals (unless there are data to indicate that they are also an insensitive model) and/or in relevant in vitro systems to further evaluate the potential for rasagiline to induce tumors of melanogenic cells.

[In a very recent examination of the individual rat data, it was discovered that a tumor listed in the summary table as a neurofibrosarcoma (detected in 1 control female) was given the differential diagnosis of amelanotic melanoma of the skin (location not otherwise specified). It was noted that "...it would take ultrastructural confirmation to make a diagnosis of amelanotic melanoma"; there was no mention of such confirmation. (Neurofibrosarcomas were detected in various tissues in other animals (total of 19); however, for none of these was the differential diagnosis of amelanotic melanoma noted.) Therefore, it is possible that there is an additional melanoma in a control animal. This observation does not alter the conclusions presented above.]

2. Dr. Roney concluded that the sponsor has adequately addressed the issue of potential genotoxic impurities by lowering the specification limit to — for — (and related impurities) and — nd to — for — — for the 1 mg tablet (the recommended clinical daily dose). These limits will result in a daily intake of — µg/day for each impurity. I agree that the sponsor's response is adequate.

3. Dr. Roney concluded that the sponsor has not adequately addressed the need for a repeat oral embryo-fetal development study in rabbits. The sponsor argued that a repeat study was not needed based on historical data from the conducting laboratory indicating a low incidence of visceral malformations, similar to that observed in the embryo-fetal study submitted. However, as noted by Dr. Roney, the incidence of visceral malformations has been determined to be substantially lower than observed in studies conducted in other laboratories (based on DSI inspections). Dr. Roney recommends that the sponsor conduct a repeat study as a Phase 4 commitment, as stated in the Approvable letter (July 2, 2004). I agree with this recommendation; however, I would recommend that if additional data are needed (either nonclinical or clinical) prior to approval, then a repeat study should be conducted prior to approval, if time permits.

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Lois Freed
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PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	21-641
Review number:	2
Sequence number/date/type of submission:	November 4, 2004
Information to sponsor: Yes (X) No ( )	
Sponsor and/or agent:	Teva Neuroscience
Manufacturer for drug substance:	Teva Neuroscience
Reviewer name:	Paul Roney
Division name:	Neuropharmacological Drug Products
HFD #:	120
Review completion date:	July 14, 2005

Drug:

Trade name: Agilect

Generic name (list alphabetically): Rasagiline mesylate

Code name: **TVP-1012, R-PAI mesylate**

Chemical name:

N-propargyl-1(R)-1-aminoindan mesylate

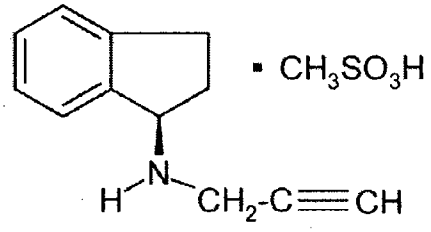
1H-inden-1-amine,2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate (CAS)

(R)-Indan-1-yl-prop-2-ynyl-amine methanesulfonate (IUPAC)

CAS registry number: 161735-79-1

Molecular formula/molecular weight: $C_{12}H_{13}N.\ CH_4SO_3$ / 267.34

Structure:



Relevant IND: IND 45,958

Drug class: Monoamine Oxidase B Inhibitor

Indication: Treatment of idiopathic Parkinson's Disease

Clinical formulation: **1 mg tablet**

Route of administration: Oral

Disclaimer: Tabular and graphical information from sponsor's submission are identified as such.

Table of Contents

Introduction

Rasagiline was submitted on September 5, 2003 for the treatment of Parkinson's disease. An Approvable Letter was issued on July 2, 2004. Among the issues the sponsor was asked to address were the three nonclinical issues identified below. This review will examine the adequacy of the Sponsor's responses to these nonclinical issues.

NONCLINICAL

1. 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 Committee meeting held on June 8, 2004.

2. AGILECT™ is a mesylate salt and, therefore, potential genotoxic impurities (e.g. — — , may arise during synthesis of the drug substance and/or during storage. In particular, the potential presence of the following in the drug substance and/or drug product is of concern:

   (a) — and related impurities) in the drug substance — These compounds are considered to have genotoxic potential based on structural alert.

   (b) — a known mutagen, in the drug substance due to the —

   (c) — in the drug product. You have demonstrated this compound to be positive in an *in vitro* Ames test.

   Ideally, the above compounds, known to be mutagenic, should be eliminated. If that is not possible, specifications should be set for each compound at — The same is true for — and related impurities); however, since we presume these to be mutagenic (i.e., mutagenicity has not been demonstrated), you may choose to directly test each of these compounds in an *in vitro* Ames assay and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing). If they are negative in these assays, there would be no need to reduce the levels to — You need to provide details of the method(s), including limits of detection and quantitation, used to evaluate each compound.

3. There is concern as to the adequacy of the oral embryo-fetal development study conducted in rabbit (— Project No. 671411). This concern is due primarily to the low incidence of external findings and a lack of visceral findings in rabbit fetuses in the study. This would suggest reduced sensitivity to detect soft tissue abnormalities, variants, etc. Unless data can be provided that adequately document the sensitivity of the methods used to assess fetal effects, the study will need to be repeated.

Figure 1, from page 9 of July 2, 2004 Approvable Letter

Rat Carcinogenicity Study

The original review of the carcinogenicity study is presented in Appendix 1 (see page 17). In this study, male rats were administered 0, 0, 0.3, 1 or 3 mg/kg/day by oral gavage for two years while female rats were administered 0, 0, 0.5, 2, 5 or 17 mg/kg/day by oral gavage. Full histopathology was conducted in the control and high dose groups only. For the low and mid dose groups, only early decedents and gross lesions were examined histopathologically in the original study; the terminally sacrificed animals were not examined histopathologically.

As noted in the original review, no significant effect on mortality was observed in either males or females. On the other hand, decreased body weight was observed at 3 mg/kg in males and 17 mg/kg in females. Since the decreases were greater than 10% at these doses, it was concluded that they exceeded the Maximum Tolerated Dose. The original review concluded that there was insufficient data to assess the carcinogenic potential of rasagiline in rats because the high doses exceeded maximum tolerated doses and the terminal sacrifice lower dose rats were not examined histopathologically. It was therefore requested that the sponsor conduct histopathology examinations on the rats from the lower dose groups. In this submission, the sponsor submitted complete histopathology results on the rats not previously examined. The number of additional rats examined per group are:

Males: Group 3 (0.3 mg/kg/day) 24
Group 4 (1.0 mg/kg/day) 22

Females: Group 3 (0.5 mg/kg/day) 23
Group 4 (2.0 mg/kg/day) 16
Group 5 (5 mg/kg/day) 20

The incidence of tumor was analyzed by Dr. Tristan Massie using trend tests and pairwise comparisons. The tumor incidences with statistical analyses are presented below.

Female Rats: Tumor Incidence and Tests for Trends (from pages 8-10 of Dr Massie's review)

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, MEDULLA	249	B-PHEOCHROMOCYTOMA	2	2	3	1	1	1	0.762/ 0.795	0.782/ 0.795
AM	ADRENAL, MEDULLA	481	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	1	0	0	0	0.560/ 0.762	0.639/ 0.747

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)
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

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)
PI	PITUITARY	429	M-CARCINOMA	0	0	0	1	0	0	0.368/ 0.484	0.486/ 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: Tumor Incidence and Tests for Trends (from pages 11-13 of Dr Massie's review)

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

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)
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-NEUROFIBROSARCOMA	0	0	0	1	1	0.248/ 0.340	0.122/ 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

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)
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 CARCINOMA	2	1	0	1	1	0.746/ 0.877	0.600/ 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

Statistical analysis indicated that there was a trend between increasing dose and benign Ovarian Granulosa Theca Cell tumors. The incidence of this tumor was relatively low (2/65 at the highest dose) and pairwise comparisons did not suggest a significant increase in incidence. The relevance of this finding for human cancer risk is uncertain. No other significant associations between rasagiline and tumor incidence were observed. On the other hand, a single melanoma was observed in a high dose male. This is an extremely rare tumor, particularly in albino rats which lack melanocytes. In a review of 1,433 (717 males and 716 females) control Sprague-Dawley rats from carcinogenicity studies over a

15 to 24 month period, only two melanomas were observed (0.14% incidence rate)[1]. In conclusion, rasagiline did not increase the incidence of tumors in rats over the course of the study. However, given the concerns about melanoma risk in patients exposed to rasagiline, the appearance of a rare melanoma in a high dose male rat is a matter of concern.

[1] Zwicker, GM, RC Eyster, DM Sells,and JH Gass (1992) Spontaneous Skin Neoplasms in Aged Sprague-Dawley Rats. Toxicol. Pathol. 20(3 part 1):327-40.

Potentially Genotoxic Impurities/Degradant

In the approvable letter, the FDA recommended that the Sponsor set specification limits of less than or equal to — for a series of potentially genotoxic impurities — (and related impurities) and — in the drug substance. The sponsor has agreed to set specifications for these substances at less than — Adequate analytical methods were developed to monitor these substances at this level.

With regards to — the sponsor has agreed to set a limit of less than — in the drug substance. However, — can also be formed as a degradant in the drug product. The Sponsor does not have an analytical method that will detect — at less than — in the drug product. The sponsor believes that — should be considered the lowest practical specification limit for the 1 mg rasagiline tablets. The resulting daily dose at this specification would be — ug/day. This is well below (more than 200-fold lower) the recommended exposure threshold of —ug/day. This reviewer considers — to be an acceptable specification limit.

In summary, the sponsor has provided adequate response to the FDA's concerns about potentially genotoxic impurities.

APPEARS THIS WAY
ON ORIGINAL

Adequacy of Rabbit Embryo-Fetal Toxicity Study

The sponsor has provided data from the laboratory which documented that there was a historically low incidence of visceral malformations in rabbits at the laboratory which conducted the study (→ . However, the low incidence of malformations at this facility stands in contrast to the experience of other laboratories conducting these assessments. It is therefore recommended that the sponsor repeat this study as a phase 4 commitment.

The sponsor has not adequately addressed the FDA concerns about the validity of the rabbit embryo-fetal toxicity study. This study will need to be repeated, possibly as a phase 4 commitment.

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Conclusions and Draft Letter Content

Three nonclinical issues were identified in the original Approvable Letter of July 2, 2004.

1 The sponsor needed to conduct full histopathological analysis of low and mid dose rats in the carcinogenicity study.
2 The sponsor needed to reduce the limits of several potentially genotoxic impurities and degradants.
3 The sponsor needed to justify the adequacy of the rabbit embryo-fetal toxicity study or to repeat the study.

The sponsor has conducted histopathological examination of low and mid dose rats in the carcinogenicity study. It was concluded that rasagiline did not cause a significant increase in the incidence of tumors in rats. However, a high dose rat was observed to have a melanoma. This is a rare tumor in Sprague-Dawley rats. The occurrence of this tumor is particularly concerning since there are concerns that rasagiline may be associated melanoma in patients taking rasagiline.

The sponsor has agreed to appropriate limits on potentially genotoxic substances. This is an adequate response to the Approvable letter.

The sponsor was not able to justify the adequacy of the rabbit embryo-fetal toxicity study. This study will need to be repeated. This reviewer feels this could be addressed as a Phase 4 commitment.

This reviewer also recommends changes to the sponsor's proposed label.

In conclusion, the Sponsor has submitted adequate data to address the nonclinical issues identified by this reviewer (in the review dated June 25, 2004). Appropriate studies have been conducted and submitted to characterize the nonclinical toxicity of rasagiline. The primary nonclinical issue in the original review is the potential carcinogenicity of rasagiline. Rasagiline increased the incidence of lung adenomas/carcinomas in male and female mice in the two year carcinogenicity study. In addition, a high dose male rat treated with rasagiline developed a melanoma in the carcinogenicity assay. This is an unusual tumor in albino rats. Rasagiline was also positive in four in vitro genotoxicity assays (three human peripheral lymphocyte assays, 1 mouse lymphoma assay). All of these data suggest that there may be potential for rasagiline to be carcinogenic in humans. The potential association of rasagiline treatment with melanoma risk is an on-going concern of the Medical Officers. The decision on whether to approve the drug will be based in part on an assessment of the potential benefits of rasagiline versus the potential risks. No other major nonclinical concerns have been identified.

This reviewer recommends that this application be approved assuming the sponsor accepts recommended changes to the label and commits to repeating the rabbit embryo-fetal toxicity study.

Draft Letter Content

APPEARS THIS WAY
ON ORIGINAL

Appendix 1- Previous Review of Rat Carcinogenicity Study

3.4.5.1 Rasagiline Mesylate (TVP-1012) Carcinogenicity Study by Oral Gavage Administration to CD®(SD)IGS BR Rats for 104 Weeks

Key study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:
1. This study only examined the incidence of tumors in high dose and control rats.
2. The high dose in both males and females exceeded the Maximum Tolerated Dose (MTD) as evidenced by an excessive loss of weight (greater than 20%).

Evaluation of tumor findings:
1. No significant increase in tumor findings were observed.
2. Since the high dose exceeded the MTD, the low and mid-dose groups should be evaluated for neoplasms to make this a valid study.

Study no.: 6751-109
Location: \tox\6751-109.pdf
Conducting laboratory and location: —
Date of study initiation: January 19, 1998
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 255495223, 255400199
CAC concurrence: The Exec CAC (May 27, 1997) recommended doses of 0.3, 1 and 3.0 mg/kg in males and 0.5, 2, 5 and 17 mg/kg in females. It was also recommended that the rats be housed individually. There was no discussion of histopathology only being conducted in control and high dose animals.

Methods

Doses: 0, 0, 0.3, 1.0, 3.0, 17.0 (females only)
Basis of dose selection (MTD, MFD, AUC etc.):
Species/strain: Rat, CD®(SD)IGS BR
Number/sex/group (main study): 65/sex/dose
Route, formulation, volume: oral gavage in distilled water, 10 mg/kg/day
Frequency of dosing: 1/day
Satellite groups used for toxicokinetics or special groups: 15/sex/dose
Age: 7 weeks
Animal housing: Individually housed in hanging wire cages
Restriction paradigm for dietary restriction studies: NA
Drug stability/homogeneity: Drug stable
Dual controls employed: Yes
Interim sacrifices: None
Deviations from original study protocol: no significant deviations

Observation times
Mortality: 2X/day
Clinical signs: 1X/day
Body weights: 1X/week (weeks 1-14), 1X/2 weeks (weeks 15-105)
Food consumption: 1X/week (weeks 1-13), 1X/2 weeks (weeks 14-104)
Histopathology: Peer review: yes (X), no ( ); Complete histopathological examination; Control and high dose only; gross lesions only at low and mid doses;
Toxicokinetics: Day 30, Week 52/53, 78; pre, 0.25, 0.5, 1, 2, 4 hours post dose; 4/rats/sex/dose
Other Studies: Prolactin and luteinizing hormone in control 1 and high dose rats during weeks 14 and 29

Results

Mortality: No statistically significant effects on mortality were observed.

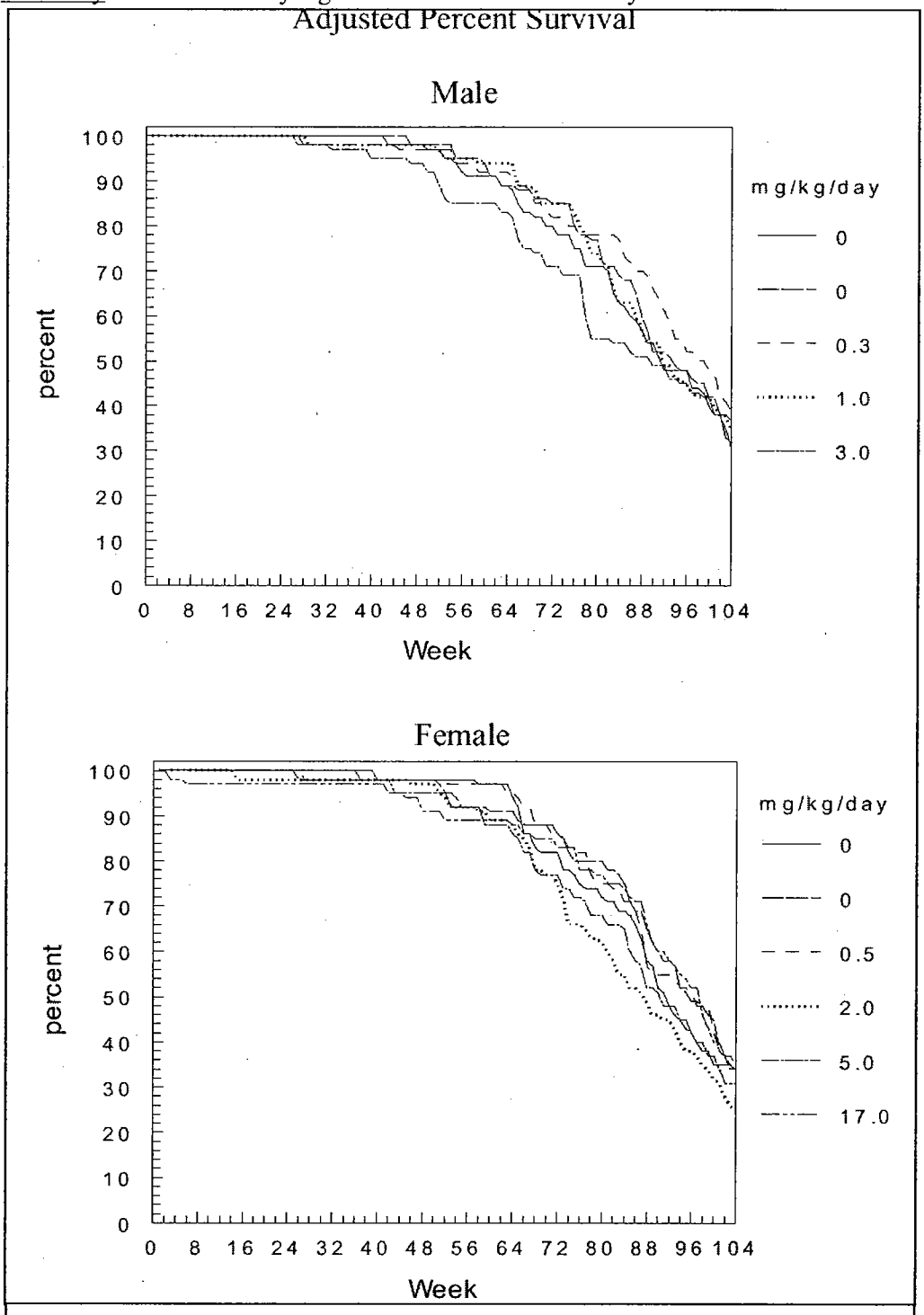


Figure 2, from page 31 of Report 6751-109

Summary of Drug-Related Clinical Observations[a]

	Male					Females					
mg/kg/day	0	0	0.3	1	3	0	0	0.5	2	5	17
Swollen Paws	11	12	17	27	37	4	2	5	20	23	15
Paw Sore/Scab	17	21	26	36	44	9	13	16	37	42	33
Aggressive Behavior	0	0	0	0	6	0	0	0	1	1	2
Hyperactivity	0	0	0	0	15	0	0	0	7	19	35
Alopecia	14	14	19	14	27	18	17	15	32	30	27
Yellow Hair Coat	10	7	11	12	6	3	7	4	7	17	30
Malocclusion	6	3	5	8	15	0	4	5	6	9	9
Red nasal discharge	1	4	2	3	4	4	6	5	2	5	12
Swollen Axillary region	2	1	3	1	2	14	11	14	12	10	4
Swollen Ventral region	14	14	14	10	3	23	20	28	21	14	5
Mass	18	10	24	13	5	39	35	36	30	28	20

a Number of animals effected.

Figure 3, from page 33 of Report 6751-109

Clinical signs:

Several clinical signs were associated with rasagiline treatment. None of these signs would be considered dose limiting.

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Body weights:

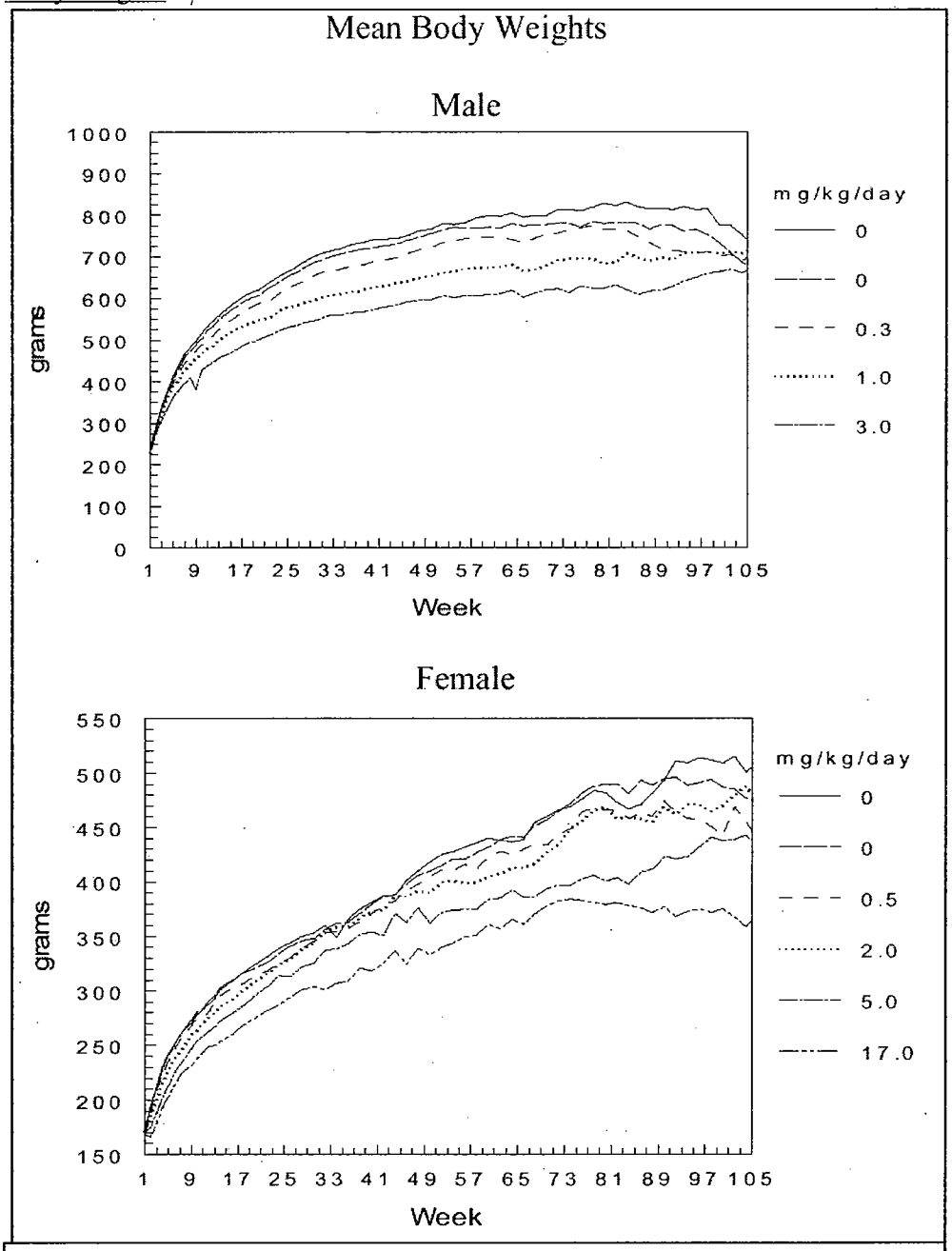

Figure 4, from page 34 of Report 6751-109

Summary of Mean Body Weights and Weights Gains (g)

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 body weight gains in grams (% difference compared to Group 1 control)					
Week 1-13	335	327 (-2%)	305 (-9%)*#	283 (-16%)*#	231 (-31%)*#
Week 1-27	453	441 (-3%)	408 (-10%) *#	362 (-20%) *#	311 (-31%) *#
Week 1-51	544	532 (-2%)	501 (-8%) *#	434 (-20%) *#	374 (-31%) *#
Week 1-77	586	552 (-6%)	542 (-8%)	469 (-20%) *#	395 (-33%) *#
Week 1-104	512	440 (-14%)	466 (-9%)	484 (-5%)	436 (-15%)

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 body weight gains in grams (% difference compared to Group 1 control)						
Week 1-13	127	131 (3%)	127 (0%)	115 (-9%) *#	104 (-18%) *#	86 (-32%) *#
Week 1-27	177	175 (-1%)	170 (-4%)	167 (-6%)	153 (-14%) *#	132 (-25%) *#
Week 1-51	251	244 (-3%)	242 (-4%)	229 (-9%)	203 (-19%) *#	172 (-31%) *#
Week 1-77	311	318 (2%)	301 (-3%)	296 (-5%)	238 (-23%) *#	214 (-31%) *#
Week 1-104	334	306 (-8%)	279 (-16%)	315 (-6%)	271 (-19%)	199 (-40%) *#

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

Figure 5, from page 35 of Report 6751-109

Excessive weight loss (>10%) was observed at 1 and 3 mg/kg in males and 5 and 17 mg/kg in females.

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Summary of Mean Total Food Consumption Values (g)

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 total food consumption in grams (% difference compared to Group 1 control)					
Week 1-13	2825	2769 (-2%)	2719 (-4%) *	2588 (-8%) *#	2396 (-15%) *#
Week 1-27	4310	4222 (-2%)	4086 (-5%) *#	3826 (-11%) *#	3594 (-17%) *#
Week 1-51	6904	6796 (-2%)	6582 (-5%) *	6057 (-12%) *#	5725 (-17%) *#
Week 1-77	9811	9660 (-2%)	9365 (-5%) *	8714 (-11%) *#	8217 (-16%) *#
Week 1-104	12665	11985 (-5%)	12238 (-3%)	11441 (-10%)*	11565 (-9%) *

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 total food consumption in grams (% difference compared to Group 1 control)						
Week 1-13	1904	1940 (2%)	1915 (1%)	1846 (-3%) *#	1743 (-8%) *#	1693 (-11%) *#
Week 1-27	2855	2891 (1%)	2894 (1%)	2808 (-2%)	2689 (-6%) *#	2653 (-7%) *#
Week 1-51	4676	4707 (1%)	4745 (1%)	4659 (0%)	4540 (-3%) #	4450 (-5%) *#
Week 1-77	6714	6901 (3%)	6806 (1%)	6655 (-1%)	6475 (-4%) #	6418 (-4%) *#
Week 1-104	8966	8906 (-1%)	9195 (3%)	8494 (-5%)	8473 (-5%)	8409 (-6%) *

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

Figure 6, from page 37 of Report 6751-109

Food consumption:

Hematology/Prolactin Levels:
No effects were observed on hematological parameters.
Female 17 mg/kg prolactin level was decreased at week 29 (146 vs 350 in controls) but not at week 14 (129 versus 127 in controls). No changes were observed in males. No significant changes were observed in luteinizing hormone in either sex at week 14 (only time examined).

Gross pathology:
Males

	0 mg/kg	0 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg
Swollen Foot	7/65	11/65	14/65	26/65	36/65
Foot Sores	12/65	19/65	24/65	32/65	38/65

Females

	0 mg/kg	0 mg/kg	0.5 mg/kg	2 mg/kg	5 mg/kg	17 mg/kg
Swollen Foot	3/65	1/65	6/65	16/65	24/65	18/65
Foot Sores	9/65	9/65	9/65	29/56	35/65	31/65

Histopathology:

Non-neoplastic:

The primary non-neoplastic findings consisted of chronic skin inflammation associated with foot sores in rats treated with 0.3 mg/kg and above in males and 2.0 mg/kg and above in females.

In addition, urogenital tract inflammation characterized by inflammation and hemorrhage of the urinary bladder with dilatation of the kidney and tules and tubular degernation was more common in rats treated with 3 mg/kg. This is a constellation of signs, which were not broken out individually, however the group incidence of these signs were higher than in other dose groups or in terminal sacrifice 3 mg/kg male rats.

Comparison of Kidney and Urinary Bladder in Early Decedents and in High Dose Terminally sacrificed Male Rats.

	0 mg/kg	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg Early	3.0 mg/kg Terminal
Kidney, tubule degeneration	2/45	1/45	0/41	3/43	11/41	1/24
Kidney, tubule dilation	4/45	2/45	3/41	3/43	13/41	0/24
Urinary bladder, acute inflammation	8/45	4/45	5/41	7/43	14/41	0/24
Urinary bladder, hemorrhage	4/45	2/45	2/41	5/43	16/41	0/24

Text Table 7. Incidences of Animals with Primary Neoplasms in All Animals

Tissue/Neoplasm	Males					Females					
Treatment Group	1	2	3	4	5	1	2	3	4	5	6
Rasagiline mesylate (TVP-1012) Base (mg/kg/day)	0.0	0.0	0.3	1.0	3.0	0.0	0.0	0.5	2.0	5.0	17.0
Brain (number examined)	(65)	(65)	(44)	(46)	(65)	(65)	(65)	(55)	(53)	(51)	(65)
M-Astrocytoma	2	–	–	–	1	1	–	–	2	1	1
M-Oligodendroglioma	–	–	–	1	–	–	–	–	–	–	–
B-Granular cell tumor	–	1	–	–	–	–	–	–	–	–	–
Thyroid	(65)	(65)	(42)	(43)	(65)	(65)	(65)	(42)	(49)	(46)	(65)
M-C cell carcinoma	–	1	1	–	1	–	–	–	–	1	1
B-C cell adenoma	4	3	3	3	6	5	6	3	3	1	2
M-Follicular cell carcinoma	1	–	1	–	–	1	3	–	1	1	1
B-Follicular cell adenoma	–	4	2	5	1	–	2	–	–	1	–
Parathyroid	(58)	(62)	(37)	(39)	(52)	(56)	(47)	(34)	(43)	(37)	(57)
B-Adenoma	–	–	–	1	–	–	–	–	–	–	–
Pancreas	(65)	(64)	(39)	(43)	(65)	(65)	(65)	(42)	(48)	(44)	(64)
M-Islet cell carcinoma	–	1	–	–	–	1	–	–	–	–	1
B-Islet cell adenoma	5	3	2	3	2	2	–	–	–	–	–
M-Acinar cell carcinoma	1	–	–	–	–	–	–	–	–	–	–
B-Acinar cell adenoma	–	–	–	–	–	–	1	–	–	–	–
M-Sarcoma, NOS	–	1	–	–	–	–	–	–	–	–	–
Spinal Cord, Lumbar	(65)	(65)	(40)	(43)	(65)	(64)	(65)	(42)	(49)	(45)	(65)
M-Astrocytoma	–	–	–	1	–	–	–	–	–	–	–
Adrenal Cortex	(65)	(65)	(43)	(44)	(65)	(65)	(65)	(52)	(58)	(53)	(65)
M-carcinoma	1	1	–	–	1	2	–	–	–	1	–
B-adenoma	1	1	–	–	2	1	1	2	1	–	–
Adrenal Medulla	(65)	(64)	(44)	(42)	(65)	(65)	(64)	(48)	(58)	(50)	(64)
M-Pheochromocytoma	5	4	2	–	2	–	–	–	–	–	–
B-Pheochromocytoma	10	8	4	2	3	2	2	1	1	1	1
Pituitary	(65)	(64)	(48)	(50)	(65)	(64)	(65)	(59)	(59)	(61)	(65)
B-Adenoma	42	51	39	30	33	57	57	56	50	56	51
M-Carcinoma	–	–	–	–	–	–	–	–	1	–	–
M-Astrocytoma (pars nervosa)	1	1	–	–	1	–	–	–	–	–	–
Thymus	(56)	(56)	(38)	(40)	(61)	(59)	(61)	(41)	(47)	(43)	(62)
M-Thymoma	–	–	–	–	–	–	–	1	1	–	–
Heart	(65)	(65)	(41)	(43)	(65)	(65)	(65)	(42)	(49)	(45)	(65)
M-Neurofibrosarcoma	–	–	–	1	1	–	–	–	–	–	–
M-Atriocaval mesothelioma	–	1	–	–	–	–	–	–	–	–	–
Jejunum	(55)	(50)	(31)	(34)	(47)	(51)	(54)	(32)	(35)	(33)	(54)
M-Carcinoma	1	–	–	–	–	–	–	–	–	–	–
Duodenum	(55)	(57)	(39)	(35)	(58)	(61)	(65)	(37)	(39)	(37)	(63)
M-Carcinoma	–	1	–	–	–	–	–	–	–	–	–

Figure 7, from page 73 of Report 6751-109

Neoplastic:

Liver	(65)	(65)	(46)	(48)	(65)	(65)	(65)	(45)	(52)	(48)	(65)
M-Hepatocellular carcinoma	–	2	3	2	–	–	1	–	–	–	1
B-Hepatocellular adenoma	1	–	–	–	–	1	–	–	–	–	–
B-Cholangioma	–	–	–	1	–	–	–	1	–	–	–
Spleen	(65)	(65)	(43)	(43)	(65)	(65)	(65)	(43)	(48)	(48)	(65)
M-Hemangiosarcoma	1	–	–	–	–	–	–	–	–	–	–
Mammary, Caudal, Female	na	na	na	na	na	(64)	(64)	(52)	(55)	(50)	(63)
M-Adenocarcinoma						5	4	5	6	1	–
B-Fibroadenoma						15	22	17	11	13	5
B-Adenoma						1	2	1	2	3	1
B-Fibroma						–	–	–	1	–	–
M-Neurofibrosarcoma						–	–	–	2	–	–
M-Sarcoma, NOS						–	–	–	1	–	–
Mammary, Cranial, Female	na	na	na	na	na	(61)	(59)	(50)	(49)	(50)	(57)
M-Adenocarcinoma						–	7	4	–	–	1
B-Fibroadenoma						20	12	12	9	12	12
B-Adenoma						–	–	–	1	–	–
M-Fibrosarcoma						–	1	–	–	–	–
Mammary, Cranial & Caudal Combined, Females	na	na	na	na	na	(64)	(64)	(52)	(55)	(50)	(63)
M-Adenocarcinoma						5	10	9	6	1	1
B-Fibroadenoma						30	27	25	18	20	15
B-Adenoma						1	2	1	3	3	1
M-Fibrosarcoma						–	1	–	–	–	–
M-Sarcoma, NOS						–	–	–	1	–	–
B-Fibroma						–	–	–	1	–	–
M-Neurofibrosarcoma						–	–	–	2	–	–
Mammary, Male	(5)	(4)	(6)	(2)	(2)	na	na	na	na	na	na
B-Fibroadenoma	–	1	–	–	–						
B-Fibroma	2	1	3	1	–						
B-Lipoma	–	–	1	–	–						
Lung	(65)	(65)	(42)	(43)	(65)	(65)	(65)	(42)	(49)	(46)	(65)
M-Leiomyosarcoma	–	–	–	–	–	–	–	–	–	–	1
Mesenteric Lymph Node	(65)	(65)	(41)	(43)	(62)	(63)	(65)	(42)	(50)	(44)	(64)
M-Hemangiosarcoma	–	1	–	1	–	–	–	–	–	–	–
B-Hemangioma	–	–	–	–	1	–	–	–	–	–	–
Kidney	(65)	(65)	(47)	(45)	(65)	(65)	(65)	(44)	(50)	(47)	(65)
M-Tubular cell carcinoma	–	1	–	–	–	–	–	–	–	–	–
M-Liposarcoma	1	–	–	–	–	–	2	–	–	–	–
B-Lipoma	–	–	1	–	–	–	1	–	1	–	–
Testis	(65)	(65)	(42)	(43)	(64)	na	na	na	na	na	na
B-Interstitial cell tumor	1	3	–	–	3						
B-Seminoma	1	–	–	–	–						

Figure 8, from page 74 of Report 6751-109

Prostate	(64)	(65)	(43)	(44)	(65)	na	na	na	na	na	na
M-Carcinoma	–	1	–	–	–						
Ovary	na	na	na	na	na	(63)	(65)	(46)	(53)	(47)	(65)
M-Sertoli cell tumor						–	1	–	–	–	–
B-Granulosa/theca cell tumor						–	–	–	–	1	2
B-Interstitial gland adenoma						–	1	–	–	–	–
Oviduct	na	na	na	na	na	(1)	(0)	(0)	(0)	(0)	(0)
B-Adenoma						1	–	–	–	–	–
Uterus	na	na	na	na	na	(64)	(65)	(50)	(53)	(50)	(65)
B-Leiomyoma						–	1	–	1	–	1
B-Endometrial stromal polyp						6	4	–	2	3	5
Uterus, Cervix	na	na	na	na	na	(64)	(65)	(43)	(49)	(46)	(65)
M-Neurofibrosarcoma						1	–	–	–	–	–
B-Leiomyoma						–	–	–	–	–	1
B-Fibroma						1	–	–	–	–	–
Vagina	na	na	na	na	na	(63)	(65)	(42)	(49)	(45)	(65)
M-Neurofibrosarcoma						1	1	–	–	–	–
Clitoral Gland	na	na	na	na	na	(1)	(0)	(0)	(0)	(0)	(1)
B-Squamous cell papilloma						–	–	–	–	–	1
Hematopoietic Neoplasia	(65)	(65)	(44)	(43)	(65)	(65)	(65)	(43)	(49)	(45)	(65)
M-Histiocytic sarcoma	3	2	4	2	–	–	1	1	1	1	2
M-Lymphoma	–	–	–	–	–	–	–	1	1	1	1
M-LGL leukemia	–	1	–	2	1	–	–	–	–	–	–
Skin, Other	(28)	(29)	(37)	(42)	(48)	(17)	(16)	(19)	(39)	(43)	(38)
M-Squamous cell carcinoma	2	1	–	1	1	–	–	–	2	–	–
M-Neurofibrosarcoma	1	–	1	1	1	2	–	2	1	–	–
M-Fibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Melanoma	–	–	–	–	1	–	–	–	–	–	–
B-Keratoacanthoma	2	3	3	1	3	–	–	–	1	–	–
B-Squamous cell papilloma	5	3	1	1	1	–	1	–	–	1	–
B-Sebaceous adenoma	–	–	–	–	2	–	–	–	–	–	–
B-Basal cell adenoma	–	–	–	–	–	–	–	–	1	–	–
B-Fibroma	–	–	3	1	1	–	–	–	–	–	–
B-Lipoma	1	–	–	–	–	–	–	–	–	–	–
Subcutaneous Tissue	(3)	(2)	(4)	(3)	(4)	(1)	(2)	(2)	(2)	(0)	(1)
M-Neurofibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Sarcoma, NOS	–	–	1	–	–	–	2	–	–	–	–
M-Fibrosarcoma	–	–	–	–	–	–	–	–	1	–	–
M-Malig. fibrous histiocytoma	–	–	–	–	–	1	–	–	–	–	–
M-Hemangiosarcoma	–	–	–	–	–	–	–	1	–	–	–
B-Fibroma	1	1	–	1	1	–	–	–	1	–	1
B-Lipoma	1	–	–	–	1	–	–	–	–	–	–
Cavity, Abdominal	(4)	(1)	(2)	(1)	(0)	(0)	(0)	(1)	(1)	(1)	(2)
N-Neurofibrosarcoma	–	–	–	–	–	–	–	–	–	–	1

Figure 9, from page 75 of Report 6751-109

Head, Coronal	(1)	(3)	(1)	(0)	(2)	(1)	(1)	(0)	(1)	(0)	(0)
M-Neurofibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Carcinoma, squamous cell	–	1	–	–	–	–	–	–	–	–	–
Oral Cavity	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
B-Squamous cell papilloma	–	–	–	1	–	–	–	–	–	–	–

(##) Numbers in parentheses represent number of animals for which that tissue was examined. For combined mammary glands (female), the number examined listed was the higher of the two individual glands.
M Malignant; Malig. Malignant
B Benign
- Incidence of zero
NOS Not otherwise specified
na non-applicable, gender specific tissue
LGL Large granular lymphocyte

Figure 10, from page 76 of Report 6751-109

FDA statistician (Tristan Massie, Ph.D.) has conducted a statistical analysis of the data from this study. At this reviewers request, the statistician has also analyzed the incidence of certain combinations of tumors (all lymphomas, all lymphomas/leukemias). These combinations were selected following the guidelines of McConnell et al. (1986).[2] The statistician concluded that there were no noteworthy increases or trends in tumor incidence.

Toxicokinetics:

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[2] McConnell, EE, HA Solleveld, JA Swenberg and GA Boorman (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Nat. Cancer Inst. 76(2):283-289.

Toxicokinetic Summary of TVP-1012

	Male			Female			
mg/kg/day	0.3	1.0	3.0	0.5	2.0	5.0	17.0
C_{max} (ng/ml)							
Day 30	19.18	77.50	345.25	50.80	250.00	687.00	3017.50
Week 26	30.93	122.25	474.00	87.10	435.75	688.75	2255.00
Week 52	54.35	159.45	717.25	67.75	458.75	914.75	2555.50
T_{max} (hr)							
Day 30	0.25	0.50	0.25	0.25	0.25	0.25	0.25
Week 26	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Week 52	0.25	0.50	0.25	0.25	0.25	0.25	0.25
$AUC_{(0-4)}$ ng*r/ml							
Day 30	25.65	91.44	446.79	48.14	234.61	761.80	3509.13
Week 26	43.75	172.32	642.40	72.89	355.75	964.79	3044.00
Week 52	58.51	233.63	829.45	72.45	394.65	1149.59	4368.05
$t_{1/2}$ (hr)							
Day 30	0.77	0.79	0.88	0.85	0.72	1.03	1.18
Week 26	1.22	1.18	1.20	0.89	1.09	1.29	1.75
Week 52	1.09	1.05	1.12	1.06	0.96	1.14	1.56

C_{max} = Maximum or peak concentration.
T_{max} = Time to achieve maximum concentration.
$AUC_{(0-4)}$ = $\int^{4} C(t)\,dt$ = area under the concentration curve [C(t)] from 0 to 4 hours.
$t_{1/2}$ = Half-life of first order (terminal) elimination.

Figure 11, from page 45 of Report 6751-109

Toxicokinetic Summary of Aminoindan

	Male			Female			
mg/kg/day	0.3	1.0	3.0	0.5	2.0	5.0	17.0
C_{max} (ng/ml)							
Day 30	14.36	43.92	104.68	38.70	133.50	263.50	811.25
Week 26	16.10	44.98	113.38	39.03	120.30	258.50	584.00
Week 52	14.22	46.52	127.00	46.52	148.00	318.25	910.25
T_{max} (hr)							
Day 30	0.50	0.50	0.50	1.00	0.50	0.50	1.00
Week 26	0.50	0.50	0.50	0.25	0.50	1.00	2.00
Week 52	1.00	1.00	1.00	0.50	0.50	1.00	2.00
$AUC_{(0-4)}$ ng.hr/ml							
Day 30	31.75	111.37	294.48	88.66	383.69	849.32	2626.43
Week 26	35.97	112.80	327.50	113.02	364.56	774.31	1845.68
Week 52	44.01	130.27	412.18	113.77	429.40	1011.89	3026.64
$t_{1/2}$ (hr)							
Day 30	2.21	2.01	2.58	1.80	2.55	3.41	3.86
Week 26	2.77	2.65	3.39	2.68	3.89	3.27	4.45
Week 52	3.05	3.49	5.01	2.82	2.94	2.83	5.74

C_{max} = Maximum or peak concentration.
T_{max} = Time to achieve maximum concentration.
$AUC_{(0-4)}$ = $\int^{4} C(t)\,dt$ = area under the concentration curve [C(t)] from 0 to 4 hours.
$t_{1/2}$ = Half-life of first order (terminal) elimination.

Figure 12, from page 46 of Report 6751-109

CONCLUSIONS

It is concluded that no significant increase in tumor incidence was observed in male or female rats. However, complete histopathological examination was conducted only on the control and high dose animals. Since the high dose exceeded the MTD, the lower

dose groups should have been examined. The sponsor will need to conduct this analysis to make this a valid study.

Appendix 2- Executive Carcinogenicity Assessment Committee Meeting Minutes-Final Mouse and Rat Studies

Executive CAC
June 8, 2004

Committee: Abby Jacobs, Ph.D., HFD-540, Acting Chair
Joseph Contrera, Ph.D., HFD-900, Alternate Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Lois Freed, Ph.D., HFD-120, Team Leader
Paul Roney, Ph.D., HFD-120, Presenting Reviewer

Author of Minutes: Paul Roney, Ph.D.

NDA 21-641
Drug Name: Rasagiline (Agilect)
Sponsor: Teva Pharmaceuticals

Mouse Carcinogenicity Study
CD-1 mice were administered rasagiline orally (by gavage) at doses of 0, 1, 15 or 45 mg/kg for two years. The mice tolerated these doses without notable toxicity. Mortality at the high dose was comparable to control values and final mean body weights were within 10% of control values. A significant positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed in male mice ($p=0.0007$). The increase in combined adenomas/carcinomas was significant in the high dose males ($p=0.0045$). There was also a near significant trend in the incidence of lung carcinomas alone in male mice ($p=0.0065$, FDA significance criteria is $p\leq0.005$ for trend tests) and a near significant increase in the incidence of combined adenomas/carcinomas in mid-dose males ($p=0.04$, FDA significance criteria is $p\leq0.01$ for pair-wise comparisons). The sponsor suggested that the incidence of lung neoplasms was within historical control range, but an examination of studies conducted within three years of this study showed that the incidence in control males was comparable to the control values in the present study. This would suggest that the increase in lung neoplasms observed in this study is above the historical control range as well. In female mice, a positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed. The trend was not statistically significant ($p=0.0071$); however, female mice had lower systemic exposure to rasagiline than males (the AUC in high dose females was 5,613 ng-hr/ml compared to 15,673 ng-hr/ml in high dose males) which would lower the probability of detecting tumors in females. It did not appear that an MTD was achieved in females.

Rat Carcinogenicity Study
Rasagiline was administered orally (by gavage) at doses of 0, 0, 0.3, 1 or 3 mg/kg in male Sprague-Dawley rats and at doses of 0, 0, 0.5, 2, 5 or 17 mg/kg in female Sprague-Dawley rats for two years. The high dose in both sexes exceeded the MTD as indicated by greater than 20% decrements in mean body weight compared to controls. No significant increase in tumor incidence was observed at the high dose. Histopathology was not conducted on a full battery of tissues in terminally sacrificed rats in the low and mid dose groups.

APPEARS THIS WAY
ON ORIGINAL

Executive CAC Recommendations and Conclusions:

Mouse carcinogenicity study: the Committee agreed that the mouse study was adequate, and concluded that the mouse study was positive for tumors in males (increased incidence of combined lung adenoma/carcinoma). There was an increase in the incidence of lung adenoma/carcinoma in females. Although the increase was not statistically significant, the Committee concluded that the finding in females should not be dismissed considering the increase in the same tumor types in male mice.

Rat carcinogenicity study: the Committee agreed that the rat study was adequate. However, the Committee could not reach a final conclusion regarding the rat study, because the high dose was associated with an excessive effect on body weight (i.e., >10% decrease in mean body weight compared to controls) in both males and females and complete histopathology was not done on the low and mid-dose groups. The Committee recommended that the sponsor conduct histopathology on the low and mid-dose groups and submit the results for evaluation.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

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/s/

Paul Roney
8/3/05 01:47:07 PM
PHARMACOLOGIST

Lois Freed
8/3/05 04:26:56 PM
PHARMACOLOGIST
Please see supervisory memo.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 7/1/04

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-641 (rasagiline mesylate, AGILECT™)

The nonclinical data for NDA 21-641 (rasagiline mesylate, AGILECT™) has been reviewed by Paul Roney, Ph.D. (6/25/04). Based on this review, Dr. Roney has made the following recommendations:

(1) for the 2-year carcinogenicity study in rats, the sponsor needs 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.

(2) the sponsor needs to more fully characterize "the circulating metabolites of rasagiline in the test species", i.e., mouse, rat, dog.

(3) the embryofetal development study in rabbits needs to be repeated "using doses between 7 and 45 mg/kg/day".

Dr. Roney has recommended that (1) and (2) be required prior to approval, and that (3) be conducted as a phase 4 commitment.

Comments:

(1) I concur with Dr. Roney's recommendation regarding the 2-year rat carcinogenicity study.

(2) Regarding the issue of circulating metabolites, it is Dr. Roney's opinion that circulating drug-related material has not be adequately characterized in the animal species used for toxicity testing (i.e., mouse, rat, dog). Dr. Roney notes that rasagiline is extensively metabolized in rat and dog, with parent compound accounting for only 11 and ≈5% of total radioactivity.

The sponsor has conducted mass balance studies in CD-1 mouse, rat, and dog. In all three species (oral doses: 1 and 45, 0.45, and 1.6 mg/kg in mouse, rat, and dog, respectively), the primary route of elimination is via the urine, with urinary radioactivity accounting for ≈75-80, 90, and 83% of total dose, respectively. According to the report of clinical Study No. SB-2001-018, "All major

and most minor metabolites of rasagiline that were found in the human urine collected 0-4 h post dose could be matched by chromatographically indistinguishable metabolites in mouse, rat, and dog urine." (In Study No. SB-2001-018, doses administered were 1.0 mg/kg p.o. in mouse and dog, 0.1 mg/kg p.o. in rat, and 2.0 mg p.o. in human.) According to the OCPB reviewer (Clinical Pharmacology/Biopharmaceutics Review, Andre Jackson, 5/13/04), 60% of dose radioactivity was eliminated in the urine in humans (total recovery, 84%); of that, <0.5% is accounted for by unchanged parent compound. These data would suggest that the *in vivo* metabolic profile in mouse, rat, dog, and human is qualitatively similar. They do not, however, address the extent of interspecies differences in exposure to circulating metabolites.

Plasma levels of rasagiline and metabolites were assessed in mouse and dog, and to a lesser extent in rat. In CD-1 mouse, circulating levels of rasagiline and various metabolites were quantitated at different time points following oral doses of 1 and 45 mg/kg. Eleven peaks (parent compound and 10 metabolites) were detected, representing ≈87-96% of total plasma radioactivity. The identified (or tentatively identified) metabolites were as follows: 3-OH-AI, AI, trans-3-OH-PAI, 3-keto-AI, 1-indanol, 1-indanone. Peaks (or "spots") 3Ac, 6b, 9, and 10 were not identified; peaks 6b and 9 each accounted for ≤5% of total plasma radioactivity. AI was the primary metabolite, accounting for ≈10-34% of total plasma radioactivity. Additional phase 2 metabolites were detected following incubation with β-glucuronidase/arylsulphatase.

In male dog, circulating levels of rasagiline and metabolites were quantitated for up to 8 hrs after a single oral dose of either 1.6 or 1.0 mg/kg (separate studies). Following the 1.6 mg/kg dose, two major and 7 minor peaks were detected. The major peak, DM3, accounted for ≈60-80% of total plasma radioactivity at 1 hr postdosing, but declined thereafter; DM1 was not detected at 1 hr postdosing, but increased over time, being the most abundant metabolite at 8 hrs postdosing (16-39% of total plasma radioactivity). Parent compound and metabolite (AI) each accounted for ≤6% of total plasma radioactivity. With enzymatic hydrolysis, the glucuronide conjugate of 3-OH-PAI (cis and trans isomers) was identified as a major circulating metabolite. Following the 1.0 mg/kg dose, circulating levels of parent compound were confirmed to be low, accounting for <6% of total plasma radioactivity. Other metabolites detected included the following: AI and 3-OH-AI (each accounting for 1-5% of sample radioactivity), 3-OH-PAI, 3-keto-AI, 1-indanol, and 1-indanone (<3% each). A large fraction (accounting for 50-80% of sample radioactivity) could not be further separated. However, following enzymatic hydrolysis, a major component of this fraction was identified as trans 3-OH-PAI, with minor components being identified as AI and rasagiline. N-dealkylation and hydroxylation followed by conjugation, and N-depropargylation were identified as primary metabolic pathways in dog.

In rat, metabolism studies focused almost exclusive on urinary metabolites. In one study, rasagiline and several metabolites (1-AI, AI, N-acetyl aminoindan, and "possibly" indan-1-one) were detected in plasma following a single 0.45 mg/kg (oral) dose. Parent compound accounted for ≈11% of sample radioactivity at 0.25 hrs postdosing.

Thus, it would seem that the sponsor has investigated, to some extent, the *in vivo* metabolic profile of rasagiline, including characterization of circulating drug-related material, in mouse and dog; minimal data on circulating metabolites were provided for rat. As noted by the clinical pharmacology reviewer, Dr. Andre Jackson, in his review (Clinical Pharmacology/Biopharmaceutics Review, 5/13/04), the *in vitro* metabolism data indicate qualitatively similar metabolic profiles in rat, dog, mouse, and human. *In vivo* data in humans indicate that rasagiline and a major circulating metabolite, 1-aminoindan (AI), together account for ≤50% of total plasma radioactivity. According to Dr. Jackson, this suggests "rapid and

extensive formation of other metabolites". Alone, AI accounts for ≈20% of total plasma radioactivity (3-12 hrs postdosing). According to the report of clinical Study No. SB-2001-018, parent compound and 8 metabolites were detected in human plasma (samples collected at 1, 2, 4, and 8 hrs postdosing). Of the 8 metabolites, AI was the most abundant, accounting for "about 6-12% of the radioactivity in the various plasma samples"; parent compound accounted for "about 7% of the radioactivity of plasma at 1 hour and even a lesser fraction of the radioactivity at later time points." According to the data from this study, parent compound and AI accounted for <20% of total plasma radioactivity.

The OCBP review team finds that "The Clinical Pharmacology and Biopharmaceutics section of NDA 21-641 is acceptable..." Additional metabolism data in humans is not being requested. The available data in the mouse, rat, dog, and human indicate that all species tested (including human) are exposed to circulating levels of parent compound and a major metabolite, AI. In addition, *in vitro* metabolism data and data on urinary metabolites would suggest qualitatively similar metabolism among all species tested (including human). Without additional data in humans for comparison, additional data in the animal species would be of limited usefulness. Therefore, it is recommended that no additional metabolism data in animals be requested.

(3) I concur that the embryo-fetal development study in rabbit needs to be repeated. However, the primary reason is that the study was conducted in 1997 by
The result of a previous DSI inspection revealed that an untrained technician was performing the fetal examinations in that laboratory during this period (cf. Pharmacologist Review of GLP EIR, CP , Michael F. Skelly, Ph.D., 4/2/99; 4/3/00). This technician was particularly deficient in evaluating visceral findings. An examination of the data from the rasagiline study indicated that no visceral findings were detected, even though >600 fetuses were examined. In the repeat study, the sponsor should carefully select doses to avoid wide gaps between doses (as Dr. Roney recommends).

Other issues:

(4) AGILECT™ is a mesylate salt and, therefore, potential genotoxic impurities (e.g., , may arise during synthesis of the drug substance and/or during storage. In particular, the potential presence of the following in the drug substance and/or drug product is of concern:

(a) (and related impurities) in the drug substance .
These compounds are considered to have genotoxic potential based on structural alert.

(b) a known mutagen, in the drug substance due to

(c) , in the drug product. This compound was positive in an *in vitro* Ames test conducted by the sponsor.

For the above compounds known or demonstrated by the sponsor to be mutagenic, the sponsor should ideally eliminate them. If that is not possible, specifications should be set for each compound at The same is true for and related impurities); however, since we presume these to be mutagenic (i.e., not demonstrated), an alternative would be for the sponsor to directly test each of these compounds in an *in vitro* Ames assay and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing). If they are negative in these assays, there would be no need to reduce

the levels tc — For each compound, the sponsor should provide a detailed description of the analytical methods used to quantify each of these compounds. The impurities issues should be resolved prior to approval.

(These impurity issues were discussed with the review chemist, William Timmer, Ph.D., and the recommendations reflect input from Dr. Timmer.)

(5) phototoxicity: It is my understanding that there is a concern regarding a possible signal for increased carcinogenic potential in humans, based on an apparent increase in the incidence of melanomas in rasagiline-treated patients. One possible mechanism underlying such a finding would be an increased sensitivity to sunlight. According to FDA's guidance on photosafety testing, the potential to absorb UVA, UVB, or visible light (290-700 nm) and distribution of drug-related material into skin and eye suggests the potential for phototoxicity. Rasagiline absorbs light with a peak at 210 nm (8973 $dm^3/cm/mol$) (tested in a range of 190-300 nm), and distribution of drug-related material into skin and eye was demonstrated in albino (maximum of 11 and 0.03% of dose radioactivity) and pigmented rats following an acute oral dose. Distribution of radioactivity into eye and skin was higher in pigmented rats as compared to albino rats (eye: 13-fold at 2 hrs postdosing, 40-fold at 24-48 hrs postdosing), and higher (2-3 fold) into pigmented skin compared to non-pigmented skin in the same animal. Depending upon the strength of the signal in humans, additional nonclinical studies may be warranted.

Labeling issues:

Carcinogenicity: the description of the 2-year carcinogenicity study in rat will be updated when the sponsor completes the microscopic analysis of tissues in the low and mid-dose groups.

Mutagenesis: for the *in vitro* mouse lymphoma tk assay, the sponsor — However, there was an increase in mutant frequency at the HC tested in the absence of metabolic activation. The increase exceeded the sponsor's minimum criterion for a positive response. The sponsor characterized the response as "equivocal" due to the "minimum" increase and the fact that an increase was only observed at the HC. Neither of these observations sufficiently supports exclusion of the finding from labeling. In addition, the HC was not associated with excessive cytotoxicity; relative growth at the HC was 20%. Also in this assay, the examination of colony sizes indicated an increase in both small and large colonies, both in the absence and presence of metabolic activation. Therefore, rasagiline would appear to be mutagenic and clastogenic in this assay.

Pregnancy Category: the findings observed in the battery of reproductive toxicology studies support a category "C", not as proposed by the sponsor. In addition, there is a lack of adequate data, i.e., an embryo-fetal development assay in rabbit and prenatal/postnatal development study (physical and behavioral development) in rat.

An examination of the data from two reproductive toxicology studies (i.e., the prenatal/postnatal development study of rasagiline in rats and the combination [rasagiline + levodopa/carbidopa] embryo-fetal development study in rabbits) raised concerns regarding the adequacy of the evaluation of rasagiline's effects on physical and behavioral development and additional adverse effects of rasagiline in combination with levodopa/carbidopa on rabbit fetuses. The concern regarding the adequacy of the evaluation of postnatal development was based on the observations that (a) 100% of all animals in all groups (including controls) achieved developmental milestones or performance criteria on 17 of 21 tasks (or trials) and that (b) performance on developmental milestones and behavioral tasks were scored as either "0" or "1" (e.g., performance in the Water

maze task was scored only as "0" = no memory or "1" = memory). Dr. Ed Fisher (reproductive toxicology expert, HFD-120) examined the methods used for behavioral assessment and concluded that some parameters were assessed too late (e.g., negative geotaxis on Day 21 instead of Days 6-12 postpartum) and that the scoring system used was insensitive.

Dr. Fisher was also asked to evaluate the external and visceral findings in rabbit fetuses from the combination embryo-fetal study because it was noted that interventricular septal defect was detected in 3 fetuses from three litters in the high-dose combination group (compared with only 2 other affected fetuses, one in the low-dose combination group and one in the levodopa/carbidopa group. Dr. Fisher concluded that there was an increase in cardiovascular abnormalities in the levodopa/carbidopa alone group and, to a greater extent, in the combination groups. Although the effect was not dose-related, the dose-related increase in total litter loss may have masked a dose-relationship. As noted, interventricular septal defect was observed only with the high-dose combination.

PARAMETER	CONTROL	RASAGILINE	LD/CD	RASAGILINE + LD/CD		
		3 mg/kg	80/20 mg/kg	0.1/80/20 mg/kg	0.6/80/20 mg/kg	1.2/80/20 mg/kg
affected fetuses	1/139	2/123	5/154	10/111	6/85	6/138
affected litters	1/17	2/16	4/19	7/19	5/13	5/16

Interspecies comparisons: safety margins based on plasma AUC (for rasagiline) were calculated using the following data:

SPECIES	STUDY	DOSE (mg/kg)	AUC (ng•hr/mL)
mouse	2-yr car	1	60*
		15	2140*
		45	15673 (M), 5613 (F)
rat	male fertility[!]	3	no data (360)
	female fertility/embryofetal development	3	351 (premating)
		3	746 (GD17)
	pre/postnatal development[#]	0.1	no data
		0.3	126 (GD17)
		1.0	204 (GD17)
	combination embryofetal development	1	136
		0.1/80/20	<LLOQ
		0.3/80/20	41
		1.0/80/20	95
rabbit	combination embryofetal development	1.2	400
		0.1/80/20	15.7
		0.6/80/20	91.2
		1.2/80/20	164
human		1 mg	12.4

*average of means for M and F; [!]no data; based on data at 5.1 mg/kg from chronic study: #no data; used data from the female fertility/embryofetal development study

Safety margins calculated for levodopa/carbidopa were based on a maximum clinical dose of 8000/200 mg/day (i.e., 4933mg/123m^2) (reference: STAT!Ref, AHFS DRUG INFORMATION®, through WEBLERN).

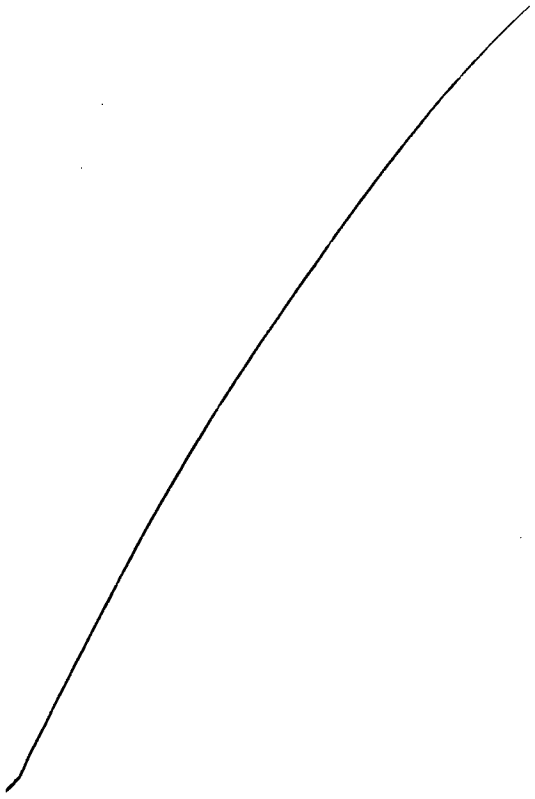
Recommendations

I concur with Dr. Roney's recommendation that NDA 21-641 is approvable from a pharmacology/toxicology standpoint. The issues regarding the 2-year rat carcinogenicity study and impurities need to be resolved prior to approval.

The sponsor needs to conduct a repeat embryo-fetal development study in rabbit. This study should be conducted prior to approval if time allows while the sponsor is addressing other pre-approval requirements. If the sponsor can adequately address other pre-approval requirements in a timely manner, or if there are no such requirements, then the embryo-fetal study may be conducted as a phase 4 commitment. In the latter case, the sponsor should commit to a timeline for completion of the study post-approval.

A need for an assessment of potential phototoxic effects of rasagiline should be considered, based on the perceived strength of the signal for carcinogenicity in humans (i.e., melanomas) and the anticipated value of mechanistic and/or other nonclinical studies in further evaluation of that signal.

Recommended Labeling



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/s/

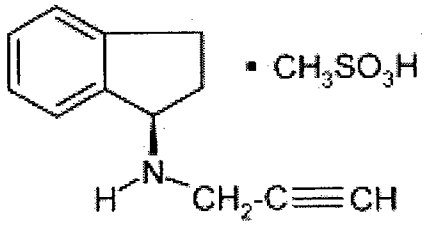
Lois Freed
7/1/04 03:55:38 PM
PHARMACOLOGIST

NDA number: 21-641
Review number: 1
Sequence number/date/type of submission: September 5, 2003
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Teva Neurosciences
Manufacturer for drug substance: Teva Neurosciences, Inc.

Reviewer name: **Paul L. Roney, Ph.D., D.A.B.T.**
Division name: **Neuropharmacological Drug Products**
HFD #: **120**
Review completion date: **June 25, 2004**

Drug:

Trade name: Agilect
Generic name: Rasagiline mesylate
Code name: **TVP-1012, R-PAI mesylate**
Chemical name:
N-propargyl-1(R)-1-aminoindan mesylate
1H-inden-1-amine,2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate (CAS)
(R)-Indan-1-yl-prop-2-ynyl-amine methanesulfonate (IUPAC)
CAS registry number: 161735-79-1
Molecular formula/molecular weight: $C_{12}H_{13}N.\ CH_4SO_3$ / 267.34
Structure:



Relevant IND: IND 45,958

Drug class: Monoamine Oxidase B Inhibitor

Indication: Treatment of idiopathic Parkinson's Disease

Clinical formulation: **1 mg tablet**

Route of administration: Oral

Proposed use: Monotherapy or combination therapy for Parkinson's Disease

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

This Reviewer recommends that this application be considered **Approvable**.

1.2 Recommendation for nonclinical studies

The sponsor has not adequately evaluated the carcinogenic potential of Rasagiline in rats. The sponsor needs to conduct histopathology on all of the low and mid dose rats in their carcinogenicity study and submit the results for evaluation. This should be done prior to approval.

The sponsor has not characterized the circulating metabolites of rasagiline in the preclinical species (mouse, rat, dog and rabbits). It is recommended that the sponsor conduct studies using radiolabel rasagiline to identify circulating metabolites. This should be done prior to approval.

The sponsor has not adequately evaluated the potential effects of rasagiline on embryo-fetal development in rabbits. The sponsor's study needs to be repeated. This may be done as a Phase IV commitment.

1.3 Recommendations on labeling

This reviewer recommends changes to the Clinical Pharmacology and the Carcinogenesis, Mutagenesis and Impairment of Fertility sections.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

Rasagiline is an MAO-B inhibitor which is proposed for the treatment of Parkinson's disease. It preferentially inhibits MAO-B over MAO-A in vivo in mice, rats and dogs. It is nearly completely metabolized in the preclinical species and the metabolites are excreted in the urine. It is carcinogenic in mice causing an increased incidence of combined lung adenomas and carcinomas in both sexes. The carcinogenic potential has not been adequately examined in rats. Rasagiline is positive in three separate in vitro chromosomal aberration studies using human lymphocytes and in another in vitro study using mouse lymphoma cells. It was negative in the Ames assay and in the in vivo mouse micronucleus test. Rasagiline had no significant effects on rat fertility or embryo-fetal development. Increased post partum pup mortality was observed in offspring of rats treated with rasagiline during pregnancy. The effects on embryo-fetal development in rabbits have not been adequately evaluated. No specific target organs were identified in repeat dose toxicity testing. The toxicity of rasagiline was increased with co-administration of levodopa/carbidopa.

2.2 Pharmacologic activity

Rasagiline is the R enantiomer of N-propargyl-1-aminoindan mesylate. It is a relatively specific inhibitor of MAO-B over MAO-A. Inhibition of MAO-B is a relevant pharmacologic activity for a potential Parkinson's disease drug. The activity resides in

the parent compound and is specific for the R-enantiomer. Both the mesylate salt and the hydrochloride salts are effective inhibitors of MAO-B in vivo and in vitro. Rasagiline is capable of crossing the blood-brain barrier and inhibiting MAO-B. The inhibition is long lasting (inhibition is observed for up to 72 hours following acute treatment). In laboratory animals, doses which cause near complete inhibition of MAO-B will also inhibit MAO-A to a lesser extent.

2.3 Nonclinical safety issues relevant to clinical use

Rasagiline appears to be well absorbed orally. It is extensively metabolized (less than 1% of administered compound is excreted unchanged). At least 14 separate metabolites were identified in rat urine. However, circulating plasma levels of the metabolites has not been completely characterized in the preclinical species (mouse, rat, dog and rabbit). Rasagiline metabolites are primarily excreted via the urine.

Rasagiline has been tested at doses up to 100 mg/kg for 13 weeks in mice, 17 mg/kg for 26 weeks in rats and 21 mg/kg for 52 weeks in dogs. Adverse effects were generally limited to body weight changes. No specific target organ toxicities were identified in these studies.

Rasagiline has been examined in an appropriate battery of genotoxicity studies. Rasagiline increased the incidence of chromosomal aberrations in human peripheral lymphocytes in three separate assays and in the mouse lymphoma assay. It was negative in the Ames assay and in the in vivo mouse micronucleus test.

Rasagiline has been examined in two year carcinogenicity assays in mice and rats. Rasagiline caused a statistically significant increased trend in the incidence of combined lung adenomas/carcinomas in male mice with a significant increase in combined lung adenomas/carcinomas in high dose male mice. A near statistically significant increase in the incidence of combined lung adenomas/carcinomas was observed in female mice. Since a significant increase in the same tumor was observed in male mice and since rasagiline is genotoxic, the increased incidence of lung neoplasms in female mice is considered biologically significant. No significant increase in the incidence of tumors was observed at the high dose in male and female rats. However, the high dose exceeded the maximum tolerated dose and the terminally sacrificed lower dosed rats were not examined histopathologically. A final conclusion on the potential carcinogenicity of rasagiline in rats can not be made until the incidence of tumors in the low and mid dose rats has been evaluated.

Rasagiline has been evaluated in a full reproductive toxicity battery. Rasagiline did not affect fertility parameters in male and female rats at doses up to 3 mg/kg. No adverse effects on embryo-fetal development were observed in rats at 3 mg/kg, a dose which induced mild maternal toxicity. In the rabbit embryo-fetal development study, fetal toxicity (as indicated by decreased fetal weight and increased embryo-fetal deaths) was observed at a frankly maternally toxic dose of 45 mg/kg. No maternal or embryo-fetal effects were observed at 7 mg/kg. The doses used in this study were not considered adequate. In embryo-fetal development studies, the high dose should cause slight maternal toxicity. In the present study, the high dose caused severe maternal toxicity which confounded the interpretation of the results. The mid dose group had n o signs of maternal toxicity, which suggests that this dose was not high enough to use as a high dose. It is recommended that this study be repeated as a Phase IV commitment using

doses between 7 and 45 mg/kg (such as 15 and 30 mg/kg). In the pre/post natal development study, rats were administered 0.2, 0.3 or 1 mg/kg. The 1 mg/kg dose caused mild maternal and offspring toxicity. No effects were observed on pup physical or behavioral development. In addition, pup fertility was unaffected.

There is a significant increase in toxicity when rasagiline is administered with levodopa/carbidopa than is observed with either drug alone in rats, dogs, and rabbits. The reason for this increased toxicity is uncertain. There does not appear to be any significant changes in the pharmacokinetics of either substance to account for the toxicity. Since some of the toxicity observed in dogs (e.g., circling behavior) could be regarded as stereotypic behavior, this toxicity may be due to excessive dopaminergic activity. This may due to increased brain dopamine levels, but this has not been definitely demonstrated.

3.1 PHARMACOLOGY/ TOXICOLOGY INTRODUCTION

3.1.1 Introduction and Drug History

Teva Neurosicences submitted this application (NDA 21-641) for Rasagiline (Ageilect) for the treatment of Parkinsons disease on September 5, 2003. The original Investigational New Drug Application (IND 45,958) was originally submitted on August 5, 1994. Rasagiline has been synthesized as the mesylate and hydrochloride salts. The sponsor has conducted pharmacological and pharmacokinetic studies which suggest that the pharmacological and toxicological characteristics of the two salts are virtually identical. In the course of this review, this reviewer will not differentiate between the two salt forms. All doses are calculated in terms of the free base. There are concerns about the potential genotoxicity of degradents products involving the mesylate salts, which will be addressed by the Chemistry Reviewer (William Timmons, Ph.D.).

This application was submitted as an Electronic Submission. In certain documents, there are discrepancies between the page numbers in the files and the page numbers expressed on the original (non-electronic) text. These discrepancies result from the sponsor adding summaries or errata pages prior to the original text in the electronic format. When this reviewer cites page numbers in this review, they refer to the electronic file pages rather than the hard copy page numbers. In most cases the page numbers will be identical.

3.1.2 List of Abbreviations Used in this Review

Acronym	Name
3-OH-PAI	3-hydroxy-1-(N- propargylamino)-indan
3-OH-AI	3-hydroxy-1-aminoindan
3-OH-AAI	3-hydroxy-1-(N-acetylamino)-indan
3-keto-AAI	3-keto-1-(N-acetylamino)-indan
3-keto-PAI, 3-PAIO	3-keto-1-(N-propargylamino)-indan, 3-N-Propargyl-aminoindan-1-one (TV-3168 is the code name for the salt)
3-keto-AI	3-keto-1-aminoindan
ADME	Administration, Distribution, Metabolism and Excretion
AGN 44A	1-N-Propargyl-1-(S)-aminoindan hydrochloride
AGN 44B	1-N-Propargyl-1-(R)-aminoindan hydrochloride
AI	1-Aminoindan, aminoindan
AUC	Area under the concentration curve
CD	Carbidopa
C_{max}	Maximum or peak concentration
CNS	Central nervous system
CV	Coefficient of Variation (Relative Standard Deviation, RSD)
DA	Dopamine
ED_{50}	Effective dose producing 50% inhibition
GC- MS	Gas Chromatography- Mass Spectrometry
IC_{50}	Inhibitor concentration causing 50% inhibition of enzyme activity
Indanol	1-indanol
Indanone, IND	1-indanone
i.p.	Intraperitoneal
i.v.	Intravenous
LD	Levodopa, l-dopa
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase type B
MAO-A	Monoamine oxidase type A
NA	Not applicable
PAI	N-Propargyl-1-aminoindan
PD	Parkinson's disease
p.o.	Oral
Rasagiline	N-propargyl-1-(R)-aminoindan
QL	Quantitation Limit
RP-HPLC	Reversed Phase- High Pressure Liquid Chromatography
s.c.	Subcutaneous
TLC	Thin Layer Chromatography
t_{max}	Time to achieve maximum concentration
TVP-101	Rasagiline hydrochloride
TVP-102,	1-N-Propargyl-1-(S)-aminoindan hydrochloride
TV-5701182B	1-N-Propargyl-1-(S)-aminoindan hydrochloride
TVP-136	(R)-1- aminoindan hydrochloride, 1-R-aminoindan hydrochloride
TVP-137	(S)-1-aminoindan hydrochloride

TVP-1012	Rasagiline mesylate, N-propargyl-1-(R)-aminoindan mesylate
TVP-1082	Racemic Rasagiline mesylate
UV	Ultraviolet

Conversion Factor from Salt to Base

Rasagiline mesylate 1.56
Rasagiline hydrochloride

3.2 PHARMACOLOGY

3.2.1 Brief summary

See page 201.

3.2.2 Primary pharmacodynamics

3.2.2.1 MECHANISM OF ACTION

3.2.2.1.1 Report on Experimental Results with Compounds 44A and 44B (Isomers Of AGN1135) Interim Report

Study: TVP-1012/ 001

Location: /pharm/ TVP-1012 001.pdf

This study examined the ability of rasagiline hydrochloride (AGN 44B) and its S-isomer (AGN 44A, TVP 102) to inhibit MAO-A and MAO-B in rat brain and human post mortem cerebral tissue. In addition, the ability of rasagiline to potentiate the tyramine pressor effect (an indication of MAO-A inhibition) was examined. These studies suggested that rasagiline is a selective MAO-B inhibitor in vitro and in vivo.

Comparison of MAO IC50's (nM) for Rasagiline, inactive isomer (TVP-102) and Racemic Mixture, in vitro study using rat brain homogenate

	Rasagiline	TVP-102	Racemic Rasagiline
MAO-B	2.5	17,000	5
MAO-A	73	26,000	140
Ratio MAO-A/MAO-B	29	1.5	28

Comparison of MAO IC50's (mg/kg) Rasagiline, inactive isomer (TVP-102) and Racemic Mixture, in vivo study. Rats sacrificed 1 and 2 hours post administration by IP injection and oral gavage, respectively.

Route	Tissue	Enzyme	Rasagiline	TVP-102	Racemic Rasagiline
IP	Brain	MAO-B	0.07	>10	0.22
		MAO-A	1.2	>10	2.5
		Ratio MAO-A MAO-B	17	---	11
	Liver	MAO-B	0.06	>10	0.11
		MAO-A	5	>10	5
		Ratio MAO-A MAO-B	83	---	45
Oral	Brain	MAO-B	0.17	>10	0.29
		MAO-A	>10	>10	>10
	Liver	MAO-B	0.05	>10	0.09
		MAO-A	>10	>10	>10

Insufficient data were presented to calculate IC50's for human cerebral MAO inhibition, but the data indicate that rasagiline is relatively specific for MAO-B (PEA as substrate) in comparison to MAO-A (5HT as substrate).

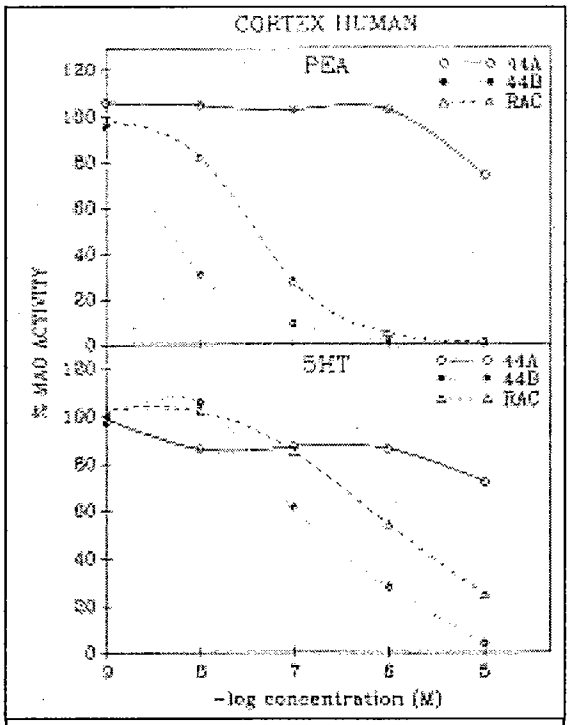


Figure 1, from page 14 of TVP-101[illegible] /001

The inhibition was irreversible. In rats administered 1 mg/kg ip, there was a rapid decrease in brain MAO-B activity with only slow recovery out to 72 hours.

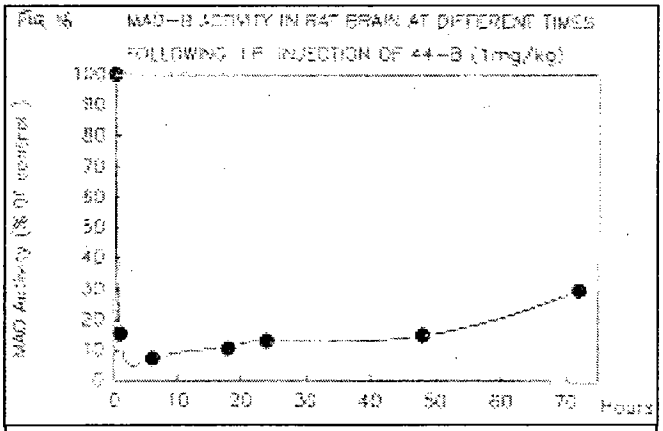


Figure 2, from page 27 of TVP-1012/ .001

Finally, 1 mg/kg ip rasagline did not potentiate the pressor effect of 50-100 ug tyramine iv in rats. This dose would be expected to inhibit MAO-A by about 50%. However, a 5 mg/kg ip dose caused about a three fold increase in the pressor reaction.

It is concluded that rasagiline is a relatively specific irreversible inhibitor of MAO-B.

3.2.2.1.2 Inhibition of MAO In Vivo - Comparison of Activity Between TVP-101 and TVP-1012

Study: TVP-1012/ 011

Location: /pharm/TVP-1012 011

This study compared the activity of the hydrochloride (TVP-101) and mesylate (TVP-1012) salts of rasagiline following oral exposure. MAO-A and -B activities in the rat brain and liver were examined two hours after oral administration. The two salts were essentially equivalent in degree of MAO inhibition. The MAO-B was inhibited by about 50% at 0.1 mg/kg while significant MAO-A inhibition was observed at about 5-10 mg/kg.

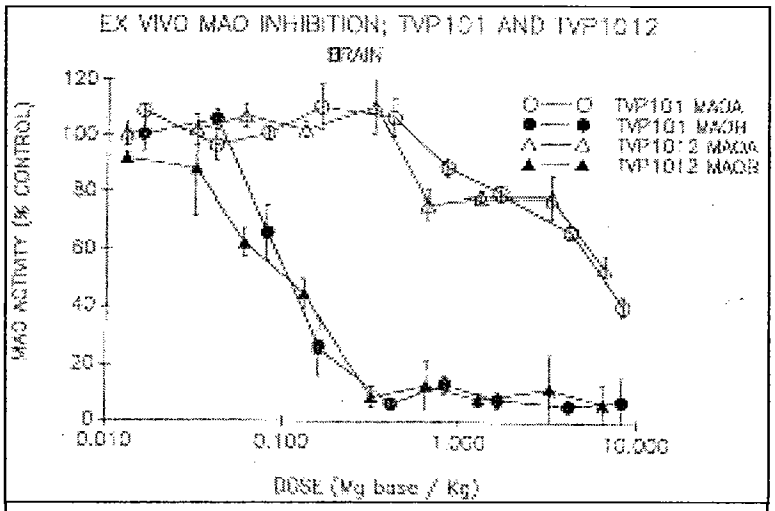


Figure 3, from page 5 of TVP-1012/ /011

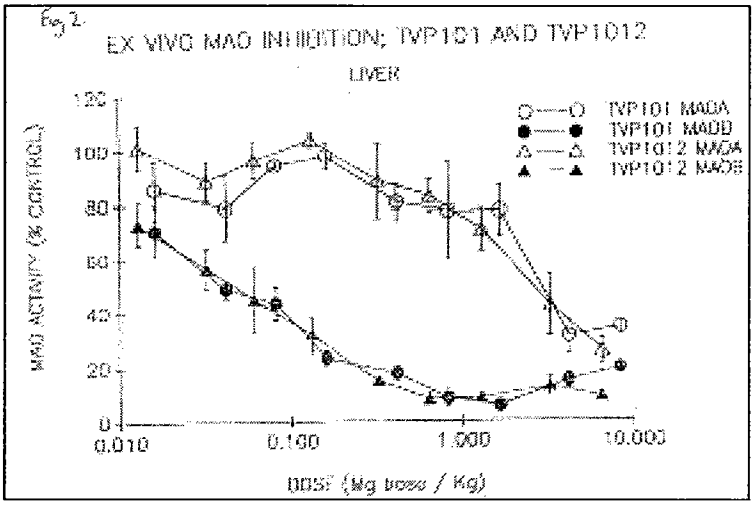


Figure 4, from page 6 of TVP-1012/ /011

3.2.2.1.3 Development of AGN-1135 (TVP-101) as an Antiparkinson Drug. Interim Report

Study: TVP-1012/ /004

Location: /pharm/ TVP-1012 004.pdf

These studies examined the specificity of rasagiline for MAO-B over MAO-A. Both the hydrochloride and mesylate salts of rasagiline had similar specificity for inhibiting MAO-B over MAO-A in rat brain homogenate (data not presented here; IC50's were not calculated). Finally, rasagiline (0.2 mg/kg sc) did not affect dopamine metabolism in the brain of rats pretreated with 6-hydroxy-DOPA in a microdialysis study. Since dopamine is metabolized by MAO-A in the rat, this suggest that rasagiline does not affect MAO-A at low doses.

3.2.2.1.4 Report On Experimental Results Of Ex Vivo MAO Activity Measured in Rat Intestine, Liver and Brain After Chronic Treatment With TVP-1012 and Deprenyl
Study: TVP-1012/ 007
Location: /pharm/ TVP-1012 007.pdf
Rats (6 males/group) were treated with 0.01-1 mg/kg/day rasagiline or deprenyl for 21 days. The rats were sacrificed and the brain, liver and intestinal MAO-A and MAO-B activity was compared to control values. The results were similar in all tissue (although intestinal MAO-B activity was less affected than liver or brain MAO-B activity). Near complete MAO-B inhibition was observed at 0.05 mg/kg. At 1 mg/kg, MAO-A activity is also inhibited by rasagiline.

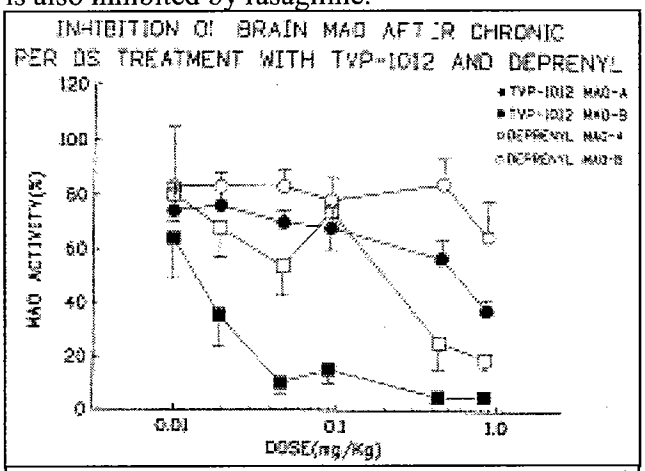


Figure 5, from page 6 of Report TVP-1012/ 007

3.2.2.1.5 Ex Vivo MAO Activity in Rat Tissues From Carcinogenicity Study of Rasagiline Mesylate (— Study No. 6751-109
Study: TVP-1012/ 016
Location: /pharm/ TVP-1012 016.pdf
Tissues (brain, liver, intestine, kidney) were collected from rats (4-8/dose) in the carcinogenicity study (see page 134) at termination and analyzed for MAO-A and MAO-B activity. The results indicate that rasagiline inhibited nearly all MAO-B activity (greater than 80% inhibition) in the various tissues at all dose levels (except the intestine at 0.5 mg/kg in females). Although there is some specificity for MAO-B at low doses (0.3-0.5 mg/kg), there was still substantial inhibition of MAO-A in all the tissues at all doses used in this study.

Table 1: MAO A and MAO B activity in female rat tissues (net-dpm)

Group	Dose	N	BRAIN dpm±sem		LIVER dpm±sem		INTESTINE dpm±sem		KIDNEY dpm±sem	
	mg/kg (base)		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
1	control	3	1619 ±688	2891 ±305	8952 ±3133	114624 3809	8452 ±412	1112 ±644	3919 ±413	3813 ±1014
3	0.5	5	183±2	542 ±17	1830 ±106	5372±4 46 *	633 ±56	170 ±17	370±3	1543 ±46
4	2	5	102±1	293±3	791 ±6	2461 ±37	366 ±23	234 ±48	240±7	705 ±11
5	5	8	61±1	109±0	584±4	1826 ±18	221±9	93±2	98±1	417±5
6	17	6	12±0	83±0	233±3	1331 ±15	-22±0	213 ±21	68±1	211±7

* One rat gave 100% inhibition, only 4 rats were included in the average

Table 2: Percent of MAO A and MAO B inhibition in female rat tissues

Group	dose	N	BRAIN % inhibition		LIVER % inhibition		INTESTINE % inhibition		KIDNEY % inhibition	
	mg/kg (base)		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
3	0.5	5	89	75	80	53	56	85	81	53
4	2	5	94	91	91	79	75	75	88	79
5	5	8	96	95	94	84	85	92	95	87
6	17	6	99	96	97	88	102	81	96	91

Figure 6, from page 5 of Report TVP-1012/ /016

Table 3: MAO A and MAO B activity in male rat tissues (net-dpm)

Group	dose	N	BRAIN dpm±sem		LIVER dpm±sem		INTESTINE dpm±sem		KIDNEY dpm±sem	
	mg/kg (base)		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
1	control	4	2593 ±749	2924 ±135	144132 ±464	10892 ±89	1296 ±468	80±54	3513 ±694	3112 ±50
3	0.3	6	181±1	638 ±25	2059 ±34	5319 ±118	1209 ±538	384± 529	618 ±14	1699 ±62
4	1	5	1331±2	22943	1749 ±49	2547 ±79	936 ±13	69± 171	507 ±24	759 ±17
5	3	4	9248	14641	1310 ±9	1742 ±43	246 ±15	-2847	401 ±8	526 ±7

Table 4: Percent of MAO A and MAO B inhibition in male rat tissues

Group	dose	N	BRAIN % inhibition		LIVER % inhibition		INTESTINE % inhibition		KIDNEY % inhibition	
	mg/kg (base)		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
3	0.3	6	93	79	86	52	7	*	82	46
4	1	5	95	92	88	76	28		86	76
5	3	4	96	95	91	84	81		89	83

* not calculated because of very low control dpm

Figure 7, from page 6 of Report TVP-1012' J16

3.2.2.1.6 Ex Vivo MAO Activity in Mouse Tissues From Carcinogenicity Study of Rasagiline Mesylate (— Study No. 6751-104)
Study: TVP-1012 — 017
Location: /pharm/TVP-1012 — 017.pdf
Tissues (brain, liver, intestine, kidney) were collected from mice (4-8/dose) in the carcinogenicity study (see page 121) at termination and analyzed for MAO-A and MAO-B activity. Tissues from concurrent control mice were not obtained, so 12 week old male mice were used as controls for both males and females. The lack of an age-matched control makes it difficult to interpret this study. There appears to be substantial inhibition of MAO-B at all dose. There also appears to be inhibition of MAO-A at the mid and high doses in all tissues (except male liver), but this reviewer can not interpret the data at the low dose with confidence without data on the MAO-A activity in aged mice. In Figures 8 and 9 below, negative MAO activity numbers indicate that there is more substrate in the mixture at the end of the incubation period than was theoretically added to the mixture at the beginning of the incubation period. This is an experimental artifact indicating near complete inhibition of enzyme activity.

Table 1: MAO A and MAO B activity in male mouse tissues (net dpm)

	Dose rasagiline	N	BRAIN dpm±sem		LIVER dpm±sem		INTESTINE dpm±sem		KIDNEY dpm±sem	
	mg/kg		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
Our Control males	-	5	6124 ±1050	4233 ±182	3520 ±1134	1545 ±93	5891 ±1833	8778 ±1881	1581 ±469	2868 ±93
Males Group 2	1	8	6±31	2101 ±231	-45 ±20	2098 ±342	604 ±247	6299 ±998	56±35	1897 ±101
Males Group 3	15	10	-6±21	320 ±32	-4±20	1495 ±759	36±29	2028 ±417	74±18	223 ±18
Males Group 4	45	4	78±3	153 ±46	-38 ±40	3658 ±1052	-123 ±5	1454 ±126	-20±8	55±19

Figure 8, from page 4 of Report TVP-1012 — 017

Table 2: MAO A and MAO B activity in female mouse tissues. (net dpm)

	Dose	N	BRAIN dpm±sem		LIVER dpm±sem		INTESTINE dpm±sem		KIDNEY dpm±sem	
	mg/kg		MAO B	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B	MAO A
Our Control males	-	5	6565 ±858	4173 ±143	3887 ±1065	1532 ±69	6533 ±1975	9593 ±1811	1671 ±430	2718 ±93
Females group 2	1	7	16±23	2555 ±159	135 ±29	2706 ±62	519 ±58	5008 ±1229	152 ±33	4336 ±183
Females group 3	15	6	16±24	258 ±69	57 ±26	460 ±73	0 ±35	2979 ±1171	71±30	362 ±72
Females group 4	45	6	47±18	105 ±67	61 ±26	167 ±82	-57 ±28	1137 ±462	36±29	491±6

Figure 9, from page 5 of Report TVP-1012/ /017

3.2.2.1.7 Report on Experimental Results of Ex-Vivo MAO Activity Measured in Mice Brain After Acute Treatment With TVP-1012.
Study: TVP-1012/ /019
Location: /pharm/TVP-1012 019.pdf
This study examined the effect of rasagiline (0.06-20 mg/kg sc) on mouse brain MAO activity. Mice were sacrificed two hours after rasagiline administration. Rasagiline preferentially inhibited MAO-B activity over MAO-A activity in mouse brain.

Table # 1 : Experiment # 1 - MAO-A activity

GROUP	DRUG	DOSE	MAO-A ACTIVITY		
		mg/kg	dpm	% activity	% inhibition
1	Saline		4369	100	0
2	TVP-1012	0.06	3960	91	9
3	"	0.6	3413	78	22
4	"	1.6	2611	60	40
5	"	3.2	1559	36	64

Table # 2 : Experiment # 1 - MAO- B activity

GROUP	DRUG	DOSE	MAO-B ACTIVITY		
		mg/kg	dpm	% activity	% inhibition
1	Saline		6326	100	0
2	TVP-1012	0.06	68	0	99
3	"	0.6	0	0	100
4	"	1.6	0	0	100
5	"	3.2	0	0	100

Table # 3 : Experiment # 2 - MAO-A activity

GROUP	DRUG	DOSE	MAO-A ACTIVITY		
		mg/kg	dpm±sd	% activity	% inhibition
1	Saline		5960±196	100	0
2	TVP-1012	5	2802±255	47	53
3	"	10	1577±138	26	74
4	"	20	856±268	14	86

Table # 4 : Experiment # 2 - MAO-B activity

GROUP	DRUG	DOSE	MAO-B ACTIVITY		
		mg/kg	dpm±sd	% activity	% inhibition
1	Saline		3960±136	100	0
2	TVP-1012	5	308±246	5	95
3	"	10	166 ± 30	3	97
4	"	20	116 ± 23	2	98

Figure 10, from page 4 of Report TVP-1012 .019

3.2.2.1.8 Ex Vivo MAO Activity in Dog Tissues From Toxicity Study of Rasagiline Mesylate (Study TVA/165-
Study: TVP-1012/ /021
Location: /pharm/TVP-1012 / 021.pdf
Tissues (brain, liver, intestine) were collected from dogs (3-6/dose) from the combination rasagiline/sinemet study (see page 87) at termination and analyzed for MAO-A and MAO-B activity. In this study, rasagiline preferentially inhibited MAO-B over MAO-A. Inhibition was reversed after an eight week recovery period.

Table 3: Percentage MAO inhibition in female dog brain, liver and intestine after administration of TVP-1012 for 13 weeks

Dose	Group	BRAIN MAO-A % inhibition	BRAIN MAO-B % inhibition	LIVER 5HT deamination % inhibition	LIVER MAO-B % inhibition	INTESTINE MAO-A % inhibition	INTESTINE MAO-B % inhibition
TVP-1012 2.0 mg/kg/day	3F	43	94	12	88	31	57
Ld/Cd 80/20 mg/kg/day TVP-1012 0.3 mg/kg/day	4F	18	94	33	85	-12	47
Ld/Cd 80/20 mg/kg/day TVP-1012 1.0 mg/kg/day	5F	39	96	30	89	0	52
Ld/Cd 80/20 mg/kg/day TVP-1012 2.0 mg/kg/day	6F	48	95	40	82	14	63
Recovery	6F	11	23	20	12	-12	18

Table 4: Percentage MAO inhibition in male dog brain, liver and intestine after administration of TVP-1012 for 13 weeks

Dose	Group	BRAIN MAO-A % inhibition	BRAIN MAO-B % inhibition	LIVER 5HT deamination % inhibition	LIVER MAO-B % inhibition	INTESTINE MAO-A % inhibition	INTESTINE MAO-B % inhibition
TVP-1012 2.0 mg/kg/day	3M	55	96	47	90	20	57
Ld/Cd 80/20 mg/kg/day TVP-1012 0.3 mg/kg/day	4M	14	94	1	76	30	63
Ld/Cd 80/20 mg/kg/day TVP-1012 1.0 mg/kg/day	5M	32	96	27	89	35	69
Ld/Cd 80/20 mg/kg/day TVP-1012 2.0 mg/kg/day	6M	46	96	25	92	46	67
Recovery	6M	1	-17	-1	-12	4	-24

Figure 11, from page 7 of Report TVP-1012/ 021

3.2.2.1.9 Development of AGN-1135 as an Antiparkinson Drug. Report at Conclusion of First Year Study (1989-1990)
Study: TVP-1012/ 002
Location: /pharm/TVP-1012 002.pdf
These studies examined the effect of rasagiline (AGN-1135) on various in vivo models of MAO-A and MAO-B inhibition. These studies suggested that rasagiline does not inhibit MAO-A at doses up to 5 mg/kg ip, but the tests for MAO-B inhibition were inconclusive.

In the first experiment, the effect of rasagiline and its inactive enantiomer (TVP-102) on DOCA-induced hypertension in unilaterally nephrectomized rats (about 4/group) was examined in two studies. Blood pressure was measured for a week in untreated rats (baseline measurements). The rats were then administered drugs by IP injection for a five (0.1 and 1 mg/kg/day) or ten (5 mg/kg/day) days with daily blood pressure measurements (treatment). The results were difficult to evaluate since the 5 mg/kg dose did not appear to affect blood pressure as much as 1 mg/kg. These doses were expected to inhibit MAO-A.

Effect of Rasagiline on Blood Pressure (mmHg) in DOCA Hypertensive Rats (1st study)

	Saline	Rasagiline		TVP-102	
		0.1 mg/kg	1 mg/kg	0.1 mg/kg	1 mg/kg
Baseline	188	188	193	189	184
Treatment	162	165	142	167	161
Difference	-26	-23	-51	-22	-23

Effect of Rasagiline on Blood Pressure (mmHg) in DOCA Hypertensive Rats (2nd study)

	Saline	Rasagiline 5 mg/kg	TVP-102 5 mg/kg	Deprenyl 1 mg/kg
Baseline	178	192	176	187
Treatment	180	176	170	180
Difference	+2	-16	-6	-7

The effects of rasagiline on 2-phenylethylamine (PEA) induced locomotor activity were examined in male rats. Rats (3-4 males/group) were pretreated with rasagiline (1 mg/kg ip), deprenyl (1 mg/kg) or saline. An hour later, rats were administered PEA (25 mg/kg ip) and activity was monitored. No significant increases in locomotor activity were observed (data not shown), although the deprenyl and rasagiline treated rats had altered behavior ("crouching expectantly with wide open eyes", page 6 of the report). Since the positive control (deprenyl) was negative in this assay too, it was concluded that the assay was insensitive for detecting in vivo MAO-B inhibition.

The effects of rasagiline on L-DOPA induced locomotor activity was examine in male rats. Rats (3-4 males/group) were pretreated with rasagiline (5 mg/kg ip), TVP-102 (5 mg/kg), deprenyl (1 mg/kg) or clorgyline (2 mg/kg). An hour later, rats were administered L-DOPA (50 mg/kg ip) and activity was monitored for two hours. No significant increases in locomotor activity were observed in rats treated with rasagiline,

TVP-102 or deprenyl, but clorgyline (an MAO-A inhibitor) caused increased locomotor activity in L-DOPA treated rats. The authors suggested that since the rat metabolizes dopamine via MAO-A, these results suggest that rasagaline does not inhibit MAO-A to an extent that dopamine metabolism would be affected.

3.2.2.1.10 Development of TVP-1012 as an Antiparkinson Drug. Annual Report
Study: TVP-1012 005
Location: /pharm/TVP-1012 005.pdf
Sprague-Dawley rats were administered rasagiline by oral or ip injection daily for 21 days. Striatal dopamine and metabolites were determined 24 hours after the last dose. When administered i.p., rasagiline did not affect the concentration of dopamine in the striatum, but the levels of dopamine's metabolites (DOPAC and HVA) were decreased. Given p.o., rasagiline increase striatal dopamine levels at doses of 2 and 5 mg/kg. There was an increased concentration of serotonin in the hippocampus and mid-brain in rasagiline-treated rats (both routes). These doses of rasagiline would be expected to inhibit MAO-A (see pages 7 and 11 for relevant data on i.p and p.o admnstration, respectively).

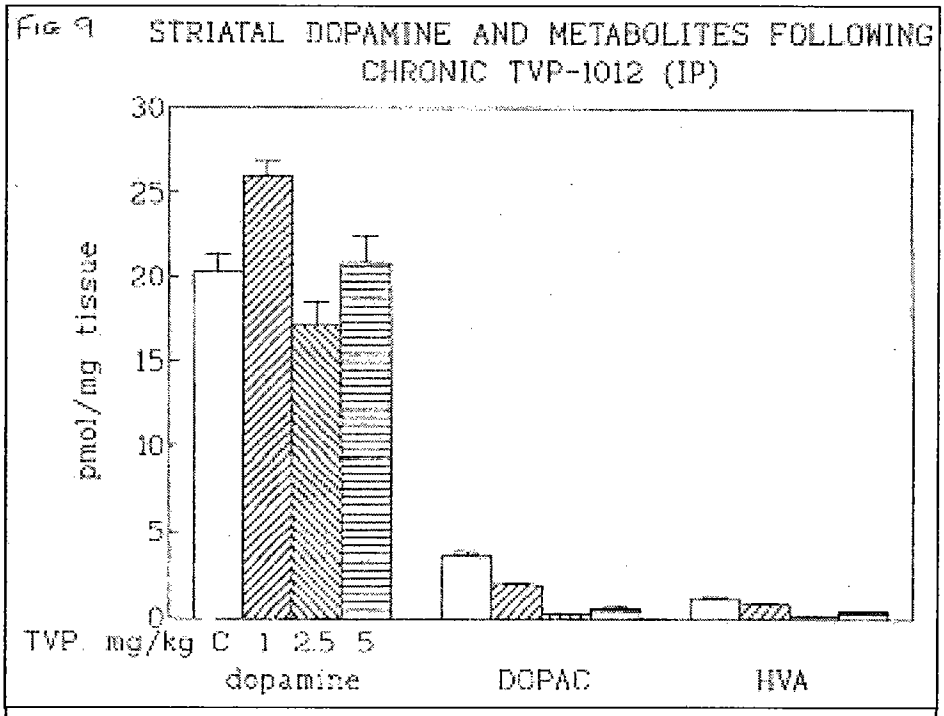


Figure 12, from page 19 of Report TVP-1012 005

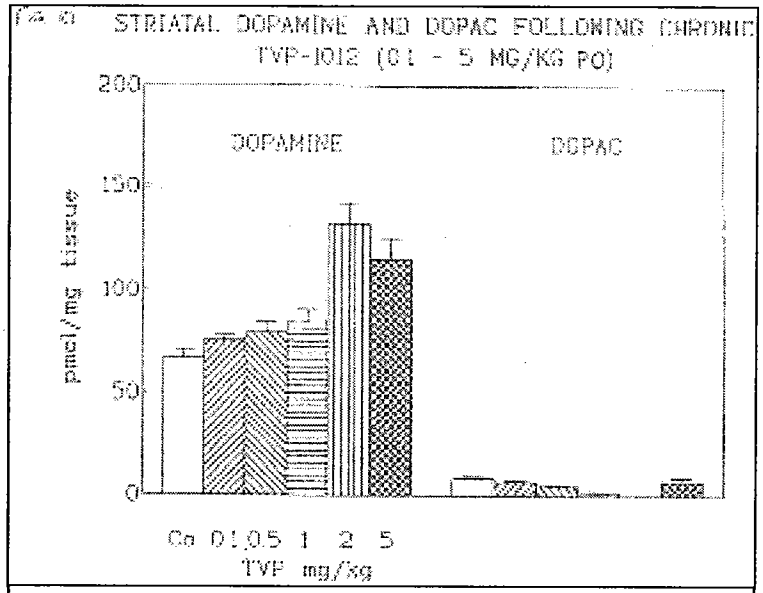


Figure 13, from page 20 of TVP-1012/ 005

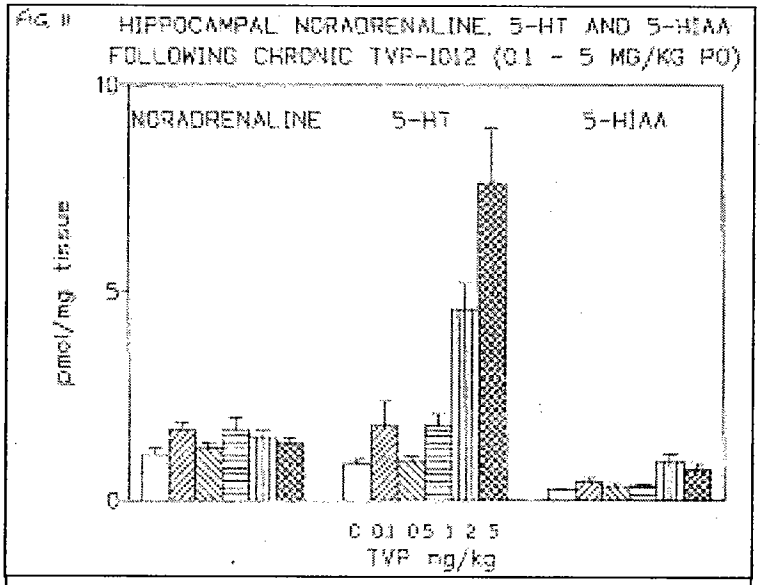


Figure 14, from page 21 of Report TVP-1012 .005

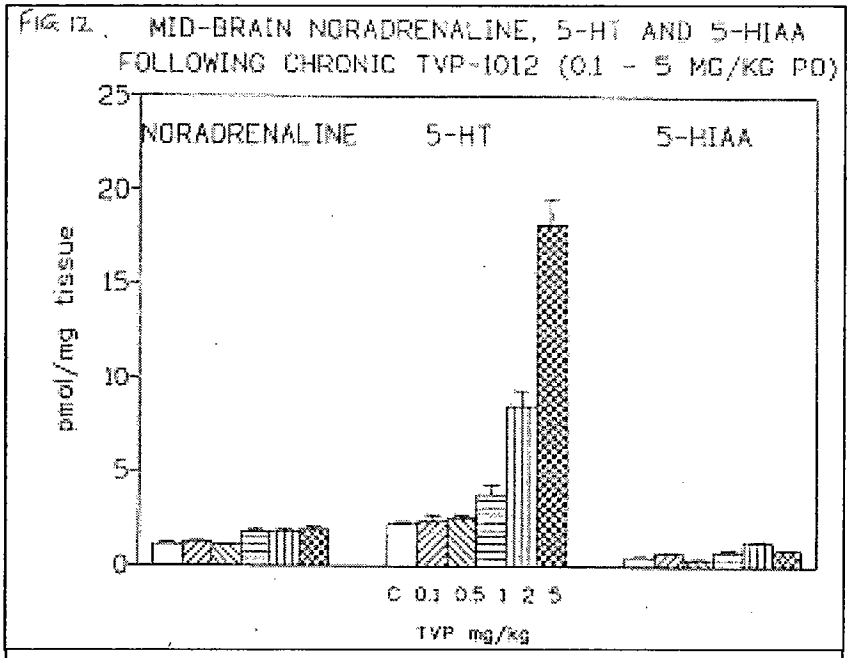


Figure 15, from page 22 of Report TVP-1012 005

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3.2.2.2 DRUG ACTIVITY RELATED TO PROPOSED INDICATION

3.2.2.2.1 Suppression of MPTP-Induced Dopaminergic Toxicity By MAO-B Inhibitors
Study: TVP-1012/ 001
Location: /pharm/TVP-1012 001
This study examined the effect of rasagiline pretreatment on MPTP-induced dopamine depletion in the striatum. Mice were administered saline, rasagiline (2.5 mg/kg), TVP-102 (2.5 mg/kg) or deprenyl (5 mg/kg) by ip injection. 60 minutes later, half of the mice were administered 30 mg/kg MPTP ip. Mice were sacrificed 7 days later and dopamine and DOPAC concentrations in the striatum were determined. Rasagiline protected against the MPTP induced dopamine depletion; the inactive enatiomer had no effect on MPTP-induced dopamine depletion. This reviewer does not regard this study as being useful in the determining the potential efficacy of rasagiline in Parkinsons disease. MPTP must be activated to the neurotoxin MPP+ via MAO-B. Since rasagiline inhibits MAO-B, it prevented the formation of the toxic intermediate. Thus, the effectiveness of rasagiline is specific to this toxin and has doubtful relevance for idiopathic Parkinsons disease.

Effect of Rasagiline pretreatment on MPTP induced dopamine depletion in the striatum (mean (SEM))

	Dopamine (ng/mg protein)		DOPAC (ng/mg protein)	
	Control	MPTP	Control	MPTP
Control	162.8 (7.2)	53.1 (6.1)	8.4 (0.5)	3.2 (0.2)
Rasagiline	185.4 (6.9)	177.9 (14.4)	7.01 (0.6)	5.95 (0.3)
TVP-102	174.8 (4.7)	59.4 (6.9)	5.57 (0.1)	3.32 (0.3)
Deprenyl	170.6 (7.0)	197.4 (8.0)	5.6 (0.3)	6.4 (0.4)

3.2.2.2.2 The Protective Effect of TVP-101 On MPTP Toxicity in Mice Striatum: Comparison With Deprenyl
Study: TVP-1012/ /002
Location: /pharm/TVP-1012 002.pdf
This study examined the effect of rasagiline pretreatment on MPTP-induced dopamine depletion in the striatum. Mice were administered saline, rasagiline (TVP-101, 0.1-2.5 mg/kg), or deprenyl (0.1-2.5 mg/kg) by ip injection. 60 minutes later, half of the mice were administered 30 mg/kg MPTP ip. Mice were sacrificed 7 days later and dopamine and DOPAC concentrations in the striatum were determined. Dopamine concentration in mice treated with MPTP alone was 70.4 ng/mg protein (data not presented on sponsor graph). Rasagiline increased the concentration of dopamine and DOPAC in MPTP treated animals to levels associated with control values. Similar degrees of change were noted in DOPAC (data are not presented). This reviewer does not regard this study as being useful in the determining the potential efficacy of rasagiline in Parkinsons disease. MPTP must be activated to the neurotoxin MPP+ via MAO-B. Since rasagiline inhibits MAO-B, it prevented the formation of the toxic intermediate. Thus, the effectiveness of rasagiline is specific to this toxin and has doubtful relevance for idiopathic Parkinsons disease.

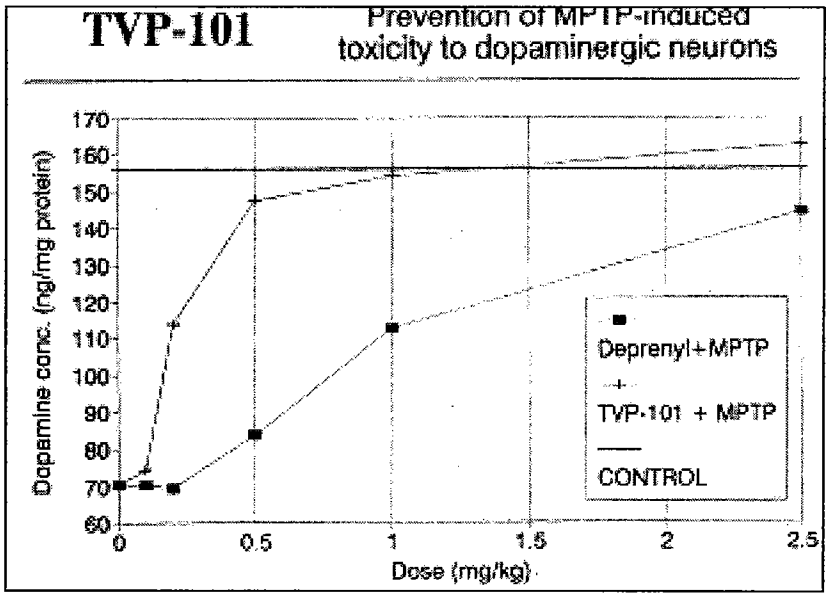

Figure 16, from page 6 of Report TVP-1012/ /002

3.2.2.2.3 The Protective Effect of TVP-101 Against MPTP Toxicity: Can TVP-101 Be Given After the Toxin?

Study: TVP-1012/ /003

Location: /pharm/TVP-1012/ /003.pdf

The aim of this study is to examine whether rasagiline (TVP-101) is effective in preventing the dopaminergic effects of MPTP when administered after the toxin. Mice (6-8/group) were injected with MPTP (30 mg/kg ip). Groups of mice were then injected with rasagiline (5 or 10 mg/kg) 0, 1, 2 or 4 hours post-injection. Controls were administered saline or MPTP alone. Mice were sacrificed seven days later and straital concentrations of dopamine and DOPAC were determined. Rasagiline was effective only when given simultaneously with MPTP. It was ineffective when given after MPTP injection. As noted previously, MPTP must be activated to the active neurotoxin MPP+ via MAO-B. Since rasagiline inhibits MAO-B, it is expected that when rasagiline is given simultaneously with MPTP, it would prevent formation of the neurotoxic metabolite preserving dopamine function in the animals.

The protective effects of TVP-101 and Deprenyl on MPTP-induced DA depletion in mice striatum

Treatment Group		DA ng/mg Protein Mean ± SEM	Dopac ng/mg Protein Mean ± SEM
1. Control		118.4 ± 3.6	5.1 ± 0.3
2. MPTP		50.8 ± 3.5[a]	3.1 ± 0.2
3. TVP-101 10 mg/kg	0 h	129.0 ± 5.4	3.8 ± 0.6
4.	1 h	46.6 ± 2.0[a]	2.0 ± 0.2
5.	2 h	43.2 ± 2.1[a]	2.0 ± 0.3
6.	4 h	50.2 ± 2.7[a]	2.1 ± 0.2
7. TVP-101 5 mg/kg	0 h	129.7 ±12.2	4.0 ± 0.6
8.	1 h	45.0 ± 2.5[a]	2.3 ± 0.2
9.	2 h	44.0 ± 2.0[a]	1.7 ± 0.3
10.	4 h	50.3 ± 3.2[a]	2.3 ± 0.3
11. Deprenyl 10 mg/kg	0 h	123.6 ± 4.0	4.6 ± 0.2
12.	1 h	95.0 ± 4.6[b]	4.0 ± 0.2
13.	2 h	58.0 ± 5.6[a]	2.4 ± 0.2
14.	4 h	43.7 ± 1.9[a]	2.5 ± 0.2

[a] $p < 0.001$ compared with control
[b] $p < 0.001$ compared with MPTP

Figure 17, from page 5 of Report TVP-1012′ 003

3.2.2.2.4 Restoration of Normal Motor Activity by TVP-1012 and TVP-1082 in Two Animal Models of Hypokinesia (A Comparative Study)

TVP-1012′ 040
/pharm/TVP-101? 040.pdf

Mice were injected rasagiline or TVP-1082 (racemic rasagiline) (1.8-15 mg/kg ip). Two hours later, the mice were administered a dopamine antagonist (haloperidol, 6 mg/kg sc). Mice were evaluated 3 hours later for behavioral indices of catalepsy (vertical rod climbing, horizontal rod grasping, and siting against wall immobility). The mice were scored on a 1-4 point scale for each test. A positive control was not used and the tests appeared to be unblinded. Rasagiline caused a dose dependent increase in activity. It is difficult to ascribe this activity to MAO-B inhibition since the mouse brain MAO-B amd MAO-A activity would be almost completely inhibited at the low dose (1.8 mg/kg) (see page 16).

In a second study, Wistar rats (4-8 males/group) were administered rasagiline or TVP-1082 (2.0-7.5 mg/kg ip). Two hours later, the rats were administered 100 mg/kg ip alpha-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor. The rats motor activity was monitored for 10 hours post dose. The 2 and 5 mg/kg rasagiline dose increased activity

to near control levels, but the high rasagiline dose (7.5 mg/kg) had lower motor activity than rats administered alpha-methyltyramine alone. This reviewer does not regard this a very specific test for determining dompminergic activity. Tyrosine hydroxylase is involved in the synthesis of epinephrine and norepinephrine. Rasagiline's effects may have been due to action of the adrenergic system rather than the dopamine system.

	TVP-1012			TVP-1082		
Dose, mg/kg	Score±SE	n	% of control	Score±SE	n	% of control
1.8	7.2±1	5	60	7.0±0.6	6	59
3.0	6.4±0.5	6	60	5.0±0.7	6	49
5.0	8.7±0.9*	6	73	6.4±0.4	6	53
7.5	11.0±0.4***	5	92	9.4±0.8**	6	78
10	11.3±0.3***	6	94	9.2±0.6***	6	77
15	10.8±0.5***	5	90	8.8±0.8*	6	73
Control saline	12±0	12	100			
Haloperidol alone	8.8±0.3	16	59			

Statistical significance with respect to haloperidol alone: * p≤0.05; ** p≤0.01; *** p≤0.001 by the Student's 't' test. The scores for (R) PAI are significantly different from those of racemic PAI at 5 mg/kg, p≤0.05; at 10 mg/kg, p≤0.01; at 15 mg/kg, p≤0.05.

Figure 18, from page 6 of Report TVP-1012' 040

	TVP-1012			TVP-1082		
Dose, mg/kg	Score±SE	n	% of control	Score±SE	n	% of control
2	14,132** ±1457	7	89	9,035 ±829	6	57
5	12,893* ±1,869	7	81	10,826* ±820	8	68
7.5	6,679 ±414	4	42	8,696 ±557	4	51
Control saline	15,862 ±1,424	5	100			
α-MpI alone	8,108** ±810	6	51			

Statistical significance by the Student's 't': * p≤0.05; ** p≤0.01; *** p≤0.001 for
Test drugs - α-MpI versus α-MpT alone
α-MpI alone versus control saline
The scores of (R) PAI versus racemic PAI are significantly different at 2 mg/kg, p≤0.01

Figure 19, from page 8 of Report TVP-1012' 040

3.2.3 Secondary pharmacodynamics

3.2.3.1 COMBINATION SCREEN DATA REPORT

Study: TVP-1012/ – 001

Location: /pharm/TVP-1012 – 001.pdf

Rasagiline was examined in a receptor/enzyme binding screen. At 10 uM, rasagiline inhibited binding to the adrenergic alpha-2b receptor by 63% and binding to the central imidazoline I2 receptor by 53%. By comparison, the IC50 for MAO-B inhibition is 0.002 uM. Complete results are presented below.

CAT. #	TARGET	BATCH	SPP.	n=	CONC.	% INHIBITION
104010	Acetylcholinesterase	51042	hum	2	10 µM	3
112200	Catechol-O-Methyltransferase (COMT)	51105	pig	2	10 µM	6
113000	Choline Acetyltransferase	51079	hum	2	100 µM	14
116010	Cyclooxygenase COX-1	52206	hum	2	10 µM	-6
193500	Free Radical Scavenger, SOD Mimetic	51075	bov	2	10 µM	-1
142000	Nitric Oxide Synthase, Constitutive (cNOS)	50916	rat	2	10 µM	7
163200	Protease, Caspase 3	51109	hum	2	10 µM	-18
171100	Protein Serine/Threonine Kinase, ERK2	50980	mouse	2	10 µM	4
178010	Protein Serine/Threonine Kinase PKC, Non-Selective	51194	rat	2	10 µM	-10
195000	Tyrosine Hydroxylase	51127	rat	2	10 µM	13
200510	Adenosine A_1	51032	hum	2	10 µM	4
200610	Adenosine A_{2A}	51033	hum	2	10 µM	5
200800	Adenosine A_3	51014	hum	2	10 µM	-11
203100	Adrenergic α_{1A}	51016	rat	2	10 µM	30
203200	Adrenergic α_{1B}	51276	rat	2	10 µM	22
203400	Adrenergic α_{1D}	51018	hum	2	10 µM	6
203620	Adrenergic α_{2A}	51019	hum	2	10 µM	38
203710	Adrenergic α_{2B}	51020	hum	2	10 µM	63
204010	Adrenergic β_1	50898	hum	2	10 µM	-3
204110	Adrenergic β_2	50899	hum	2	10 µM	6
204410	Adrenergic, Norepinephrine Transporter	50874	hum	2	10 µM	15
212500	Bradykinin B_1	50958	hum	2	10 µM	10
212610	Bradykinin B_2	50948	hum	2	10 µM	-5
214510	Calcium Channel Type L, Benzothiazepine	50902	rat	2	10 µM	-2
214600	Calcium Channel Type L, Dihydropyridine	50950	rat	2	10 µM	0
216000	Calcium Channel Type N	50959	rat	2	10 µM	7

Figure 20, from page 6 of Report TVP-1012/ 001

CAT. #	TARGET	BATCH	SPP.	n=	CONC.	% INHIBITION
						-100 -50 0 50 100
						%
219500	Dopamine D_1	51022	hum	2	10 µM	-2
219600	Dopamine D_2	51023	hum	2	10 µM	6
219800	Dopamine D_3	51025	hum	2	10 µM	10
219900	Dopamine $D_{4.2}$	51026	hum	2	10 µM	-1
220320	Dopamine Transporter	50875	hum	2	10 µM	-7
224010	Endothelin ET_A	51047	hum	2	10 µM	-5
224300	Endothelin ET_B	51048	hum	2	10 µM	24
225500	Epidermal Growth Factor (EGF)	51071	hum	2	10 µM	13
226010	Estrogen ERα	50962	hum	2	10 µM	2
226400	GABA Transporter	50964	rat	2	10 µM	-1
226500	$GABA_A$, Agonist Site	51029	rat	2	10 µM	6
226600	$GABA_A$, Benzodiazepine,					
	Central	50881	rat	2	10 µM	6
226510	$GABA_B$	51030	rat	2	10 µM	-2
232010	Glucocorticoid	51130	hum	2	10 µM	-6
232700	Glutamate, Kainate	50926	rat	2	10 µM	3
232810	Glutamate, NMDA, Agonism	50928	rat	2	10 µM	15
232910	Glutamate, NMDA, Glycine	50929	rat	2	10 µM	-3
233000	Glutamate, NMDA,					
	Phencyclidine	51049	rat	2	10 µM	-5
239510	Histamine H_1, Central	50883	gp	2	10 µM	-9
239700	Histamine H_2	50907	gp	2	10 µM	-1
239800	Histamine H_3	50914	rat	2	10 µM	-7
241000	Imidazoline I_2, Central	51050	rat	2	10 µM	53
243510	Interleukin IL-1α	50931	mouse	2	10 µM	-7
250510	Leukotriene B_4	51052	hum	2	10 µM	-14
250600	Leukotriene D_4	50954	gp	2	10 µM	-15
252600	Muscarinic M_1	51057	hum	2	10 µM	2
252700	Muscarinic M_2	51058	hum	2	10 µM	4
252800	Muscarinic M_3	51059	hum	2	10 µM	-6
257000	Neuropeptide Y_1	50997	hum	2	10 µM	11
257110	Neuropeptide Y_2	50939	hum	2	10 µM	-4
258600	Nicotinic Acetylcholine,					
	Central	50884	rat	2	10 µM	-10
260110	Opiate δ	51031	hum	2	10 µM	-4

Figure 21, from page 7 of Report TVP-1012[illegible]001

CAT. #	TARGET	BATCH	SPP.	n=	CONC.	% INHIBITION
260210	Opiate κ	51032	hum	2	10 µM	2
260410	Opiate µ	51033	hum	2	10 µM	-3
264500	Phorbol Ester	50911	mouse	2	10 µM	6
265000	Platelet Activating Factor (PAF)	51053	rabbit	2	10 µM	18
265600	Potassium Channel [K_{ATP}]	50944	syn	2	10 µM	-1
268700	Purinergic P_{1}	51034	rabbit	2	10 µM	5
268810	Purinergic P_{2}	51078	rat	2	10 µM	3
271110	Serotonin 5-HT_{1A}	51035	hum	2	10 µM	30
271650	Serotonin 5-HT_{2A}	51036	hum	2	10 µM	14
271910	Serotonin 5-HT_{3}	51038	hum	2	10 µM	11
274020	Serotonin Transporter	50877	hum	2	10 µM	-4
278110	Sigma σ_{1}	50891	hum	2	10 µM	-7
278200	Sigma σ_{2}	51358	rat	2	10 µM	9
279510	Sodium Channel, Site 2	51041	rat	2	10 µM	9
255510	Tachykinin NK_{1}	51072	hum	2	10 µM	-11
285010	Testosterone	50946	rat	2	10 µM	-4

Figure 22, from page 8 of Report TVP-1012/ 001

3.2.3.2 PHARMACOLOGY OF TVP-101. REPORT AT CONCLUSION OF SECOND YEAR'S STUDY (1990-1991)
Study: TVP-1012/ 003
Location: /pharm/TVP-1012 003.pdf
This report examined the effects of rasagiline on various systems. At 100 uM, Rasagiline inhibited acetylcholine or histamine action on the guinea pig ileum or rabbit duodenum, but no effects were noted at lower doses (10 uM) Rasagiline potentiated the pressor effects of tyramine at 10 mg/kg PO, but not at 5 mg/kg PO; rasagiline also potentiated the tyramine pressor effect at 5 and 10 mg/kg ip. No potentiation of the tyramine effect was observed following 0.1 or 0.5 mg/kg/day for 21 days. Finally, rasagiline did not inhibit raclopride binding to dopamine D2 receptor at 100 uM, although there was significant inhibition at 1000 uM (about 90% inhibition of binding).

3.2.4 Safety pharmacology

3.2.4.1 NEUROLOGICAL EFFECTS

3.2.4.1.1 Rasagiline Mesylate Irwin Test in Rats Following Oral Administration

Study: TVA 148/003273

Location: /pharm/TVA 148003273.pdf

Male rats (6/dose) were administered 0.12, 0.5 or 2 mg/kg rasagiline. Behavior was assessed at 30, 90, 150 and 300 minutes post administration.

No abnormalities were observed at any time point.

3.2.4.1.2 Assessment of Rasagiline Effects on Spontaneous and Cocaine-Induced Locomotor Activity in Mice

Study: TVP-1012/NIDA/001

Location: /pharm/TVP-1012NIDA001.pdf

Male Swiss Webster mice (8/group) were administered 0, 3, 10, 30 or 100 mg/kg by ip injection. At 20 minutes post injection, locomotor activity was assessed for 1 hour. In a separate study, mice were administered 0, 10, 30 or 100 mg/kg ip. At 20 minutes post injection, mice were administered 20 mg/kg cocaine ip and locomotor activity was assessed for 1 hour.

When rasagiline was administered alone, there was a dose-dependent decrease in activity starting at about 10 mg/kg. When rasagiline was given in combination with cocaine, there was a dose dependent decrease in cocaine induced ambulation. Since rasagiline by itself causes decreased ambulation, it is difficult to interpret the significance of this finding. It may be concluded that rasagiline does not potentiate the locomotor activity associated with cocaine, but no conclusion may reached on other potential effects of cocaine.

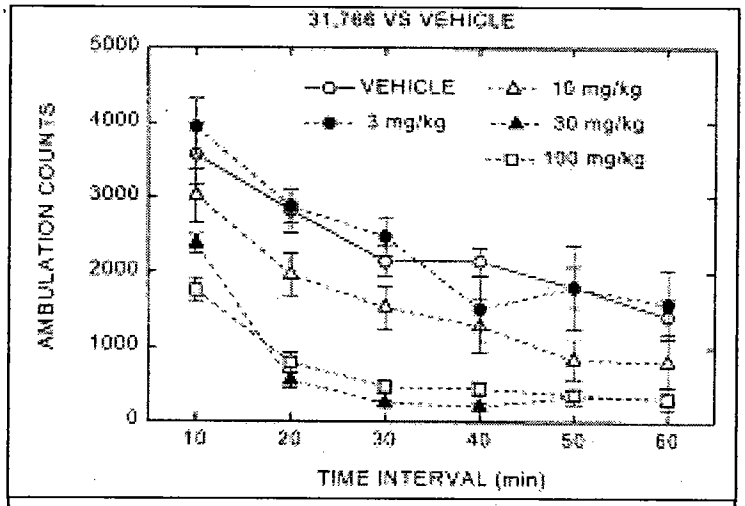

Figure 23, from page 4 of Report TVP-1012/NIDA/001

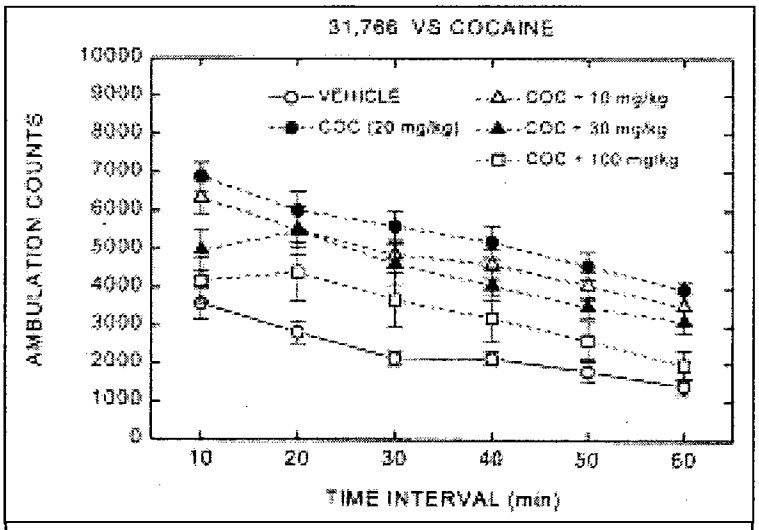

Figure 24, from page 5 of TVP-1012/NIDA/001

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3.2.4.2 CARDIOVASCULAR EFFECTS

3.2.4.2.1 Rasagiline Mesylate (TVP 1012) Telemetric Evaluation of Cardiovascular Effects in the Conscious Dog Following Oral Administration

Study TVA 147/003839

Location: /pharm/TVA 147003839.pdf

Four dogs (2/sex) were administered 0 or 3 mg/kg in a crossover study. There was a seven day washout between doses. Dogs were monitored telemetrically for 2 hours predose and 24 hours post dose. ECG and blood pressure variables were measured every 15 minutes. Both Bazett and Fridericia correction factors were applied to the QT intervals.

No effects were observed on heart rate, blood pressure or ECG parameters.

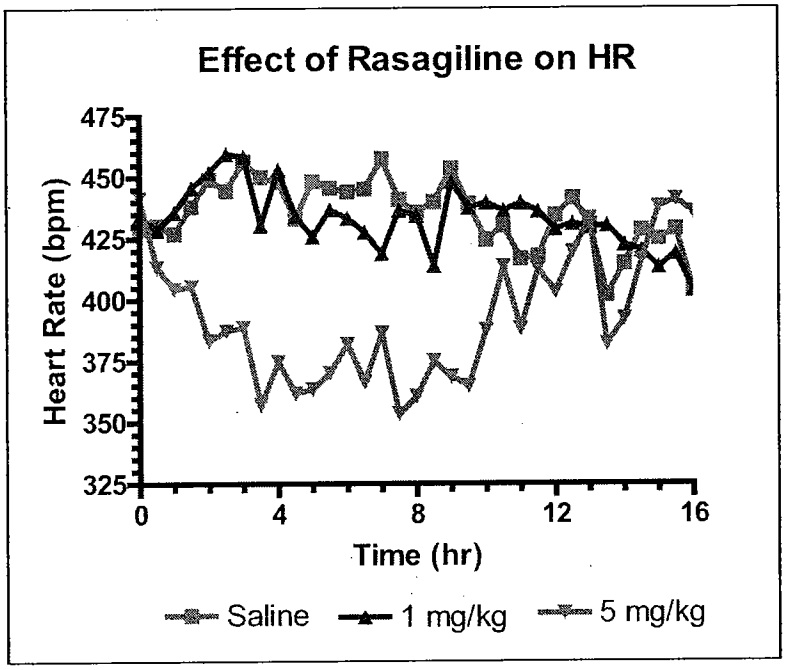
3.2.4.2.2 Cardiovascular Profile of TVP-1012, TVP-136 & TVP-137 After Intravenous Administration to Conscious Wistar Rats

Study TVP-1012/ /006

Location: /pharm/TVP-1012 006.pdf

Rats were administered 0 (13 rats), 1 (5 rats) or 5 (7 rats) mg/kg IV rasagiline. Rats were also administered 5 mg/kg IV of TVP-136 (R-1-aminoindan HCl) or TVP-137 (S-1-aminoindan HCl). The blood pressure and heart rate were monitored using an indwelling catheter.

Rasagiline did not have any effects on blood pressure. Heart rate appeared to be depressed at 5 mg/kg IV starting at about 2 hours post injection and returning to normal at about 11-12 hours post injection. TVP-136 did not affect heart rate or blood pressure.



Pulmonary effects:

No studies submitted.

3.2.4.3 RENAL EFFECTS

3.2.4.3.1 Effect of TVP-1012 and Its Combination with Levodopa/Carbidopa on the Excretion of Urine in the Rat

Study: 1999-177

Location: /pharm 1999-177.pdf

Sprague-Dawley rats (4 males/group) were dosed orally administered rasagiline or levodopa/carbidopa (see table below) for 10 days.

Dose Group	TVP-1012 dose (mg base/kg)	Carbidopa dose (mg/kg)	Levodopa dose (mg/kg)	Dose concentration (mg/ml) TVP-1012	Carbidopa	Levodopa
D1	3	-	-	0.6	-	-
D2	-	20	80	-	4	16
D3	3	20	80	0.6	4	16
D4	3	20*	80	0.6	4*	16
C**	-	-	-	-	-	-

*For group D4, Carbidopa was administered 2 hours prior to the administration of TVP-1012 and Levodopa.

** Control group was created with the vehicle, 0.5 % aqueous solution of methylcellulose.

Figure 25, from page 11 of Report 1999-177

Rat urine production was monitored daily and for 48 hours post dosing cessation. Hematology parameters were monitored on Day 10.

The combination of rasagiline and levodopa/carbidopa exceeded the MTD as indicated by decreased body gain on Day 12 in rats treated with the combination (D3 and D4). One group D4 rat died 46 hours after cessation of treatment. This rat was reported to have renal medullar tubular epithelial cell necrosis (only the kidney was examined histopathologically). Rasagiline may have decreased HVA excretion on days 10-12 of the study; but rats treated with levodopa/carbidopa had significantly increased HVA excretion. Rasagiline had no effect on water consumption or urine production. Levodopa/carbidopa increased water consumption and urine production. No effects on urine parameters were observed. Rats treated with the combination of rasagiline and levodopa/carbidopa had increased hematocrit values, but no other abnormalities were observed.

Figure 5: Body weight gain at different dose groups

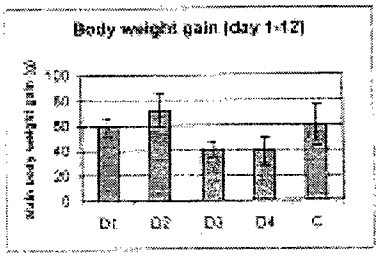


Figure 6: Body weight of animals in different dose groups

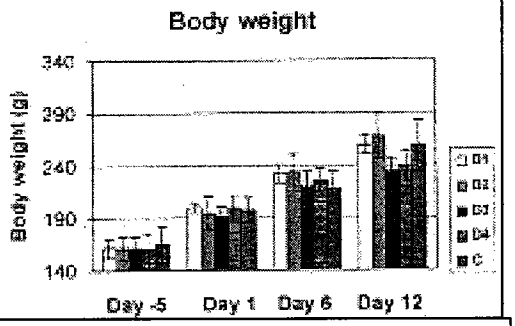
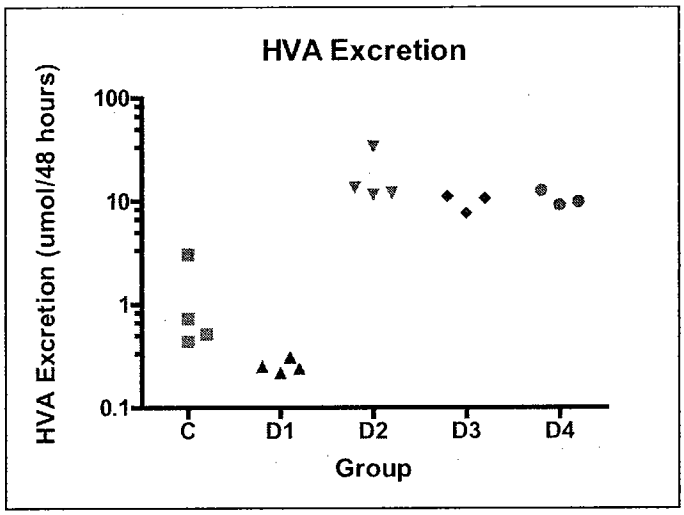


Figure 26, from page 20 of Repor' 1999-177



Gastrointestinal effects:
No studies submitted.

Abuse liability:
No studies submitted.

Other:
No studies submitted.

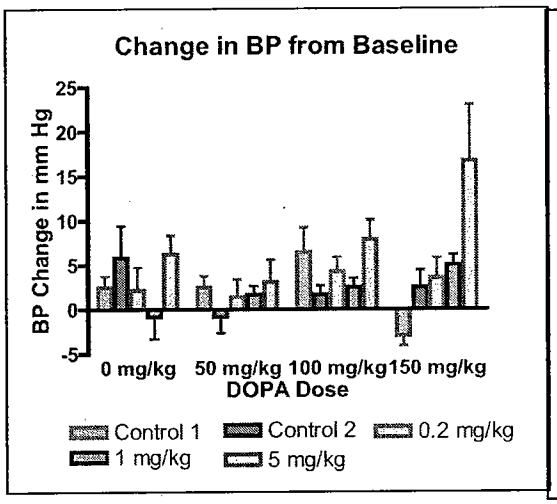
3.2.5 Pharmacodynamic drug interactions

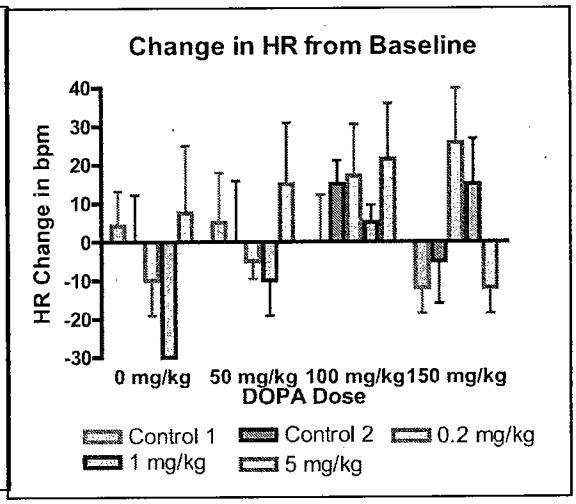
3.2.5.1 MODIFICATION OF CARDIOVASCULAR RESPONSES TO ORALLY ADMINISTERED L-DOPA BY TVP-1012, DEPRENYL AND CLORGYLINE

Study: TVP-1012/ 009

Location: /pharm/TVP-1012 009.pdf

This study examined the potential interaction between rasagiline and L-DOPA. Blood pressure and heart rate were determined in rats (6-8 males/group) via a tail catheter. Rasagline (0-5 mg/kg po) was administered. Two hours later, blood pressure and heart rate were determined. Rats were orally administered increasing doses of L-DOPA (50, 100 and 150 mg/kg) and blood pressure and heart rates were determined 30 minutes post dose. The highest dose of rasagiline (5 mg/kg) increased the blood pressure in rats treated with 150 mg/kg L-DOPA. No significant interaction effects were observed on heart rate.





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3.2.6 Metabolite pharmacological activity

3.2.6.1 THE EFFECTS OF TVP-136 AND TVP-137 ON MAO-A AND MAO-B ACTIVITIES
Study: TVP-1012')04A
Location: /pharm/ TVP-1012)04A.pdf
This study examined the effects of the rasagiline metabolites TVP-136 and TVP-137 on MAO-A and MAO-B activity. The in vitro and ex vivo studies suggest that the metabolites would not be expected to affect either MAO-A or MAO-B activity.

Rasagiline and its Metabolites Inhibition of Rat Brain MAO-A and MAO-B

	MAO-B		MAO-A		
	IC50 (nM)	Ratio to rasagaline IC50	IC50 (nM)	Ratio to rasagaline IC50	Ratio MAO-A/MAO-B IC50's
Rasagiline	10	1	900	1	90
TVP-136	20,000	2,000	75,000	83	37
TVP-137	350,000	35,000	150,000	167	0.42

Table 2: Ex-vivo inhibition of liver MAO-A (substrate 5-HT) and MAO-B (substrate PEA) following acute administration of TVP-136 and TVP-137 to rats.

		% Inhibition		
Dose (mg/kg, p.o.)		10	50	100
Molecule	MAO form			
TVP-136	MAO-B	37.7 ± 12.6	35.0 ± 0.25	38 ± 2.9
	MAO-A	9.4 ± 4.4	4.5 ± 10.5	5.7 ± 5.0
TVP-137	MAO-B	-4.2 ± 1.9	12.1 ± 2.2	11.3 ± 10.9
	MAO-A	6.0 ± 7.4	12.2 ± 7.4	8.2 ± 6.7

Table 3: Ex-vivo inhibition of brain MAO-A (substrate 5-HT) and MAO-B (substrate PEA) following acute administration of TVP-136 and TVP-137 to rats.

		% Inhibition		
Dose (mg/kg, p.o.)		10	50	100
Molecule	MAO form			
TVP-136	MAO-B	2.6	2.3	1.2
	MAO-A	10.6	4.9	-46.4
TVP-137	MAO-B	-44.7	-39.9	-40.4
	MAO-A	-48.6	-41.9	-43.5

Figure 27, from page 4 of Report TVP-1012)04A

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary
See page 203.

3.3.2 Absorption
3.3.2.1 MASS BALANCE AND PROFILING OF METABOLITES IN PLASMA AND URINE OF MICE TREATED WITH A SINGLE ORAL DOSE OF RASAGILINE MESYLATE
Study: 2001-039
Location: /pk/ 2001-039.pdf

Mice were administered 1 or 45 mg/kg PO radiolabeled rasagiline. Doses appeared to be based on doses used in the mouse carcinogenicity study.
The urine was the primary route of excretion of radiolabel.

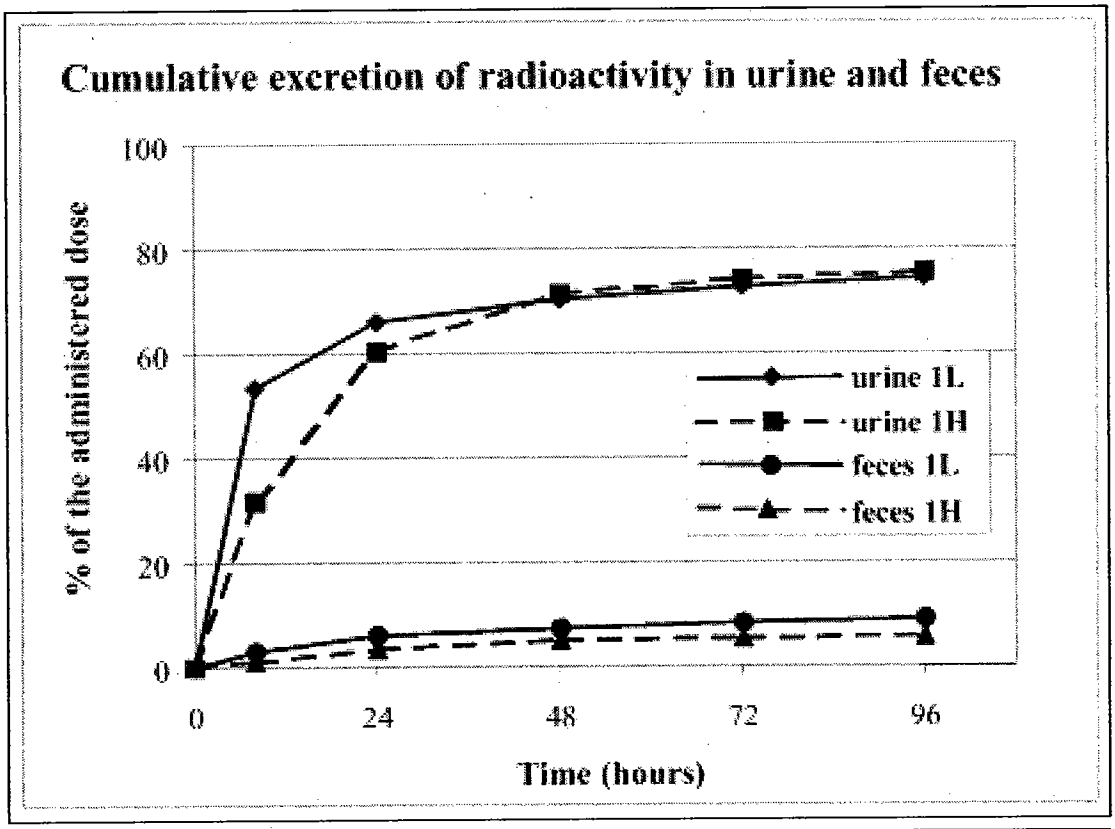

Figure 28, from page 26 of Report 2001-039

Most of the excreted radioactivity was highly polar compounds that could not be separated (spots 1 and 2 in the figure below). Spot 6 is AI and accounts for 8-19% of the administered dose. Spot 3 was 3-hydroxy-AI and accounted for 5-7% of the administered dose. Other metabolites accounted for less than 5% of the administered dose.

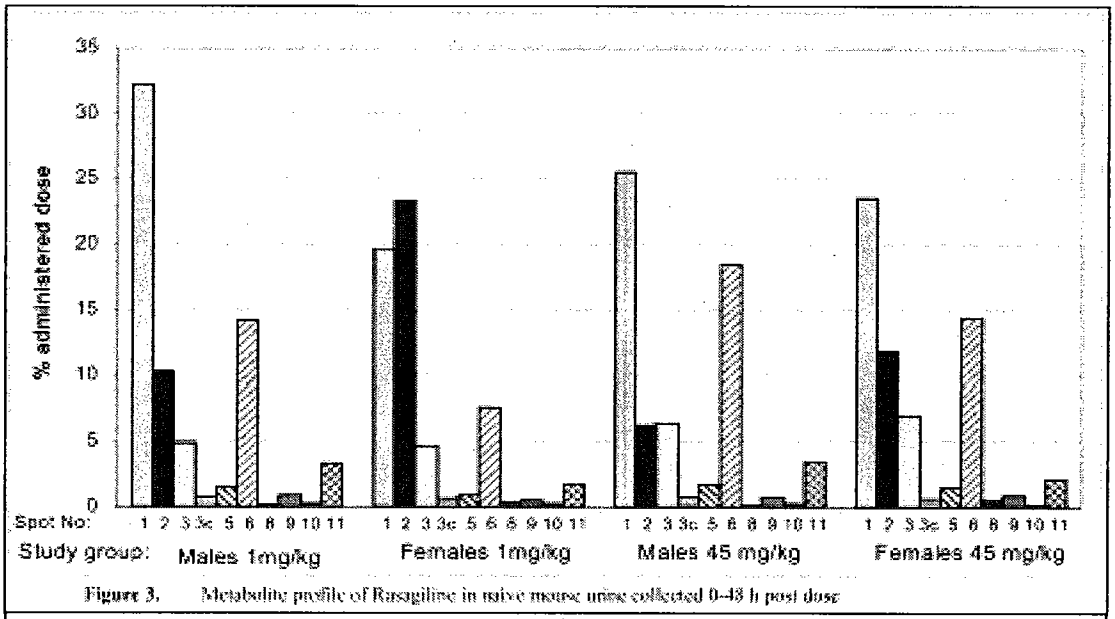

Figure 3. Metabolite profile of Rasagiline in naive mouse urine collected 0-48 h post dose

Figure 29, from page 29 of Report 2001-039

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The plasma kinetics of rasagiline and selected metabolites in male mice (only sex tested) are presented below (PAI is rasagiline).

Table 31. Pharmacokinetic parameters of rasagiline and its selected metabolites

Parameter	*Identification:* Group	3-OH-AI*	AI	Trans 3-OH-PAI	PAI
C_{max}	2L	< 21	44	7.2	57
(ng/ml)	2H	< 264	2118	262	1770
T_{max}	2L	NA	1.00	0.25	0.25
(h)	2H	NA	1.00	1.00	0.50
$AUC_{0-8\ h}$	2L	< 91	133	18	65
(h x (ng/ml))	2H	< 1655	10612	789	6659
C_{max} / Dose	2L	< 20	42	7.0	55
(ng/ml)/(mg/kg)	2H	< 6	48	5.9	40
$AUC_{0-8\ h}$ / Dose	2L	< 88	129	18	63
(h x (ng/ml)/(mg/kg)	2H	< 37	236	18	149

* The exact values could not be determined for 3-OH-AI due to an interfering component.

NA – not applicable

Figure 30, from page 70 of Report SB-2001-039

However, these components do not account for most of the circulating radioactivity. The total rasagiline equivalents identified in the above table are 307 and 19,715 ng-hr/ml for 1 and 45 mg/kg, respectively. The pharmacokinetic parameters of total radioactivity (derived from Table 26 on page 65 of this report) are presented below. Dividing the AUC for the identified metabolites above by the AUC for total radioacivity below, it is determined that the sponsor has identified 28% and 46% of the circulating metabolites at 1 and 45 mg/kg, respectively.

Pharmacokinetics of Radiolabel Rasagiline in Male Mice

Dose	$AUC_{(0-8)}$ ng eq-hr/ml	Cmax (ng eq/ml)	Tmax (hour)
1 mg/kg	1,098	472	0.25
45 mg/kg	42,463	8,159	0.5

Percentage of Circulating Radiolabel Accounted for by Identified Metabolites

Metabolite	1 mg/kg	45 mg/kg
PAI (parent)	5.9%	15.7%
AI	12.1%	25.0%
3-OH-PAI	1.6%	1.9%
3-OH-AI	<8.3%	<3.9%
Total	28.0%	46.4%

It is concluded that rasagiline is rapidly metabolized and accounts for 5.9% and 15.7% of circulating radiolabel at 1 and 45 mg/kg, respectively. However, the circulating levels of rasagiline metabolites have not been adequately characterized.

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3.3.2.2 PAI N-PROPARGYL-1(R)-AMINOINDAN (PAI) THE BIOAVAILABILITY OF PAI FROM TWO DIFFERENT SALT FORMS AFTER SINGLE ORAL DOSES TO RATS
Study: TVA 66/050593
Location: /pk/TVA 66050593.pdf
This study examined the relative bioavailability of the hydrochloride and mesylate salts of rasagiline. Rats (3/sex/timepoint) were administered 0.7 mg/kg po. Plasma levels of rasagiline (PAI) and one of its metabolites (TVP-136, aminoindan) were monitored in the plasma at 0.25, 0.5,k 0.75, 1, 2, 3, 4, 6, 8, 12 and 24 hours post dose. The two salt forms were equivalent in Cmax and AUC parameters for both parent and metabolite.

Maximum mean plasma concentrations of PAI (Cmax), their times of occurrence (Tmax) and areas under the mean plasma PAI concentration-time curves estimated to be the last sampling time at which concentrations were above the limit of quantification (AUC_t)

Parameter	Hydrochloride salt		Mesylate salt		Ratio (hydrochloride/mesylate)		
	Males	Females	Males	Females	Males	Females	All animals
Cmax (ng/ml)	14.2	19.9	11.1	29.0	1.28	0.69	0.85
Tmax (hours)	0.25	0.5	0.5	0.25	-	-	-
AUC_t (ng.h/ml)	21.4	19.1	17.8	27.7	1.20	0.69	0.89

Figure 31, from page 24 of Report TVA 66050593

Maximum mean plasma concentrations of AI (Cmax), their times of occurrence (Tmax) and areas under the mean plasma AI concentration-time curves estimated to be the last sampling time at which concentrations were above the limit of quantification (AUC_t)

Parameter	Hydrochloride salt		Mesylate salt		Ratio (hydrochloride/mesylate)		
	Males	Females	Males	Females	Males	Females	All animals
Cmax (ng/ml)	22.0	36.7	21.5	35.9	1.02	1.02	1.02
Tmax (hours)	0.5	0.75	0.75	0.5	-	-	-
AUC_t (ng.h/ml)	90.0	109.8	67.5	112.4	1.26	0.98	1.11

Figure 32, from page 25 of Report TVA 66050593

3.3.2.3 TVP-1012: A COMPARATIVE DETERMINATION OF PLASMA LEVELS OF PROPARGYL-1-AMINOINDAN (PAI) AND 1-AMINOINDAN (AI) FOLLOWING SINGLE ORAL, INTRAPERITONEAL OR SUBCUTANEOUS ADMINISTRATION OF RASAGILINE MESYLATE IN THE RATS

Study: B45pk' -98

Location: /pk/B45pk -98.pdf

The purpose of this study is to compare the bioavailability of rasagiline (1 mg/kg) via various routes of exposure (po, ip, sc). Rats (9 males/route) were administered 1 mg/kg po, ip or sc. Plasma levels of rasagiline (PAI) and its main metabolite (TVP-136, AI, aminoindan) were monitored in the plasma at 0, 2, 5, 10, 15, 30, 60, 120, 180 and 300 minutes post dose. Rasagiline had better bioavailability via subcutaneous or interperitoneal injection than via oral adminstration.

Table 1: PK parameters of PAI in rat plasma following administration of 1 mg/kg TVP-1012 by three different routes

Route	C_{max} (ng/mL)	T_{max} (min)	AUC_{0-5h} (ngxmin/mL)	$AUC_{0-\infty}$ (ngxmin/mL)	$T_{1/2}$ (min)	λ_z (1/min)
Oral	59.07	15	3952	4263	89	0.0078
I.P.	119.4	5	8623	9144	71	0.0098
S.C.	217.4	15	16090	16705	70	0.0100

Figure 33, from page 16 of Report B45pk -98

Table 2: PK parameters of AI in rat plasma following administration of 1mg/kg TVP-1012 by three different routes

Route	C_{max} (ng/mL)	T_{max} (min)	AUC_{0-5h} (ngxmin/mL)	$AUC_{0-\infty}$ (ngxmin/mL)	$T_{1/2}$ (min)	λ_z (1/min)
Oral	48.3	30	8714	13466	194	0.0036
I.P.	34.7	120	6287	10208	194	0.0036
S.C.	25.8	120	5583	7638	130	0.0053

Figure 34, from page 17 of Report B45pk -98

Table 3: Metabolite Ratios between AI and PAI with three routes of administration of TVP-1012 (1 mg/kg)

Route	AUC_∞ ratio * (mole/mole)
Oral	4.06
I.P	1.44
S.C.	0.59

*-Molecular weight of PAI=177 gr/mole
Molecular weight of AI=133 gr/mole

Figure 35, from page 18 of Report B45pkRSG-98

3.3.2.4 N-PROPARGYL-1(R)-AMINOINDAN (PAI) THE BIOAVAILABILITY OF N-PROPARGYL-1(R)-AMINOINDAN (PAI) FROM TWO DIFFERENT SALT FORMS AFTER SINGLE ORAL DOSES TO DOGS

Study: TVA65/040593

Location: /pk/TVA 65040593.pdf

This study examined the relative bioavailability of the hydrochloride and mesylate salts of rasagiline at a dose of 0.7 mg/kg free base po. Dogs (3/sex) were dosed with the salts in a cross-over experiment. Plasma samples were taken at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 7, 8, 12 and 24 hours post dose. There was a seven day washout between experiments. No particular differences in Cmax, AUC or Tmax were observed.

Effect of Salt form on parent and a selected metabolite (TVP-136) PK parameters

	Rasagiline			TVP-136		
	HCl	Mesylate	Ratio	HCl	Mesylate	Ratio
Cmax (ng/ml)	31.7	34.5	0.92	25.9	28.7	0.90
AUC (ng-hr/ml)	43.0	41.4	1.04	99.0	86.4	1.14
Tmax (hr)	1.0	1.0	---	1.5	1.2	---

3.3.3 Distribution

3.3.3.1 [^{14}C]-TVP-101 THE ABSORPTION, DISTRIBUTION AND EXCRETION IN RATS
Study: /TVA 58/930525
Locaton: /pk fVA58930525.pdf
Male albino and pigmented rats were administered 0.45 mg/kg radiolabelled rasagiline po.
Radiolabel was primarily excreted via the urine (about 90%). The feces was a minor route of excretion (about 5%).
It was rapidly distributed to the tissues (maximum tissue concentrations were generally about 15 minutes post dose).

Tissues ranked in descending order of maximal radioactivity content

Ranking	Tissue	Maximum % dose	Time of occurrence (h)
1	Muscle	24.11	0.25
2	Liver	13.20	0.25
3	Skin	11.30	0.25
4	Small intestine	8.76	0.25
5	Fat	8.47	0.25
6	Stomach	4.73	0.5
7	Whole-blood	4.54	0.25
8	Kidneys	3.89	0.25
9	Large intestine	1.88	1
10	Lungs	1.46	0.25
11	Lymph nodes	1.40	0.5
12	Brain	1.01	0.25
13	Testes	0.60	0.5,1.2
14	Lachrymal glands	0.53	2
15	Pancreas	0.49	0.25
16	Salivary glands	0.49	0.25
17	Spleen	0.39	0.25
18	Bone marrow	0.38	0.5
19	Heart	0.24	0.25, 0.5
20	Thymus	0.20	0.25, 1
21	Urinary bladder	0.18	0.5
22	Prostate	0.06	0.25, 0.5
23	Eyes	0.03	0.5
24	Adrenals	0.03	0.25
25	Thyroid	0.03	1
26	Pituitary	0.01	0.25, 0.5

Figure 36, from page 31 of Report fVA 58930525

When rasagiline was administered to pigmented rats, the concentration of rasagiline in the eye was 13-fold higher than in albino rats. Concentrations in other organ were comparable between the strains.

Rasagiline was rapidly metabolized. At 15 minutes post-administration, only 11% of circulating metabolite was chromatographically similar to unchanged rasagiline. One of the components was similar to TVP-136 ((R)-1-aminoindan); full identification of metabolites was not performed in this study.

3.3.3.2 [^{14}C]-TVP-101 STUDIES OF PLASMA PROTEIN BINDING IN VITRO (MOUSE, RAT, DOG AND MAN)
Study: TVA 108/951876
Location: /hpbio/hupharm/TVA108951876.pdf
The in vitro binding of rasagiline was determined by ultrafiltration in vitro.

The *in vitro* binding of ^{14}C-TVP101 to mouse, rat and dog plasma proteins at various concentrations by ultrafiltration

Species	Target concentration (ng/ml)	% ^{14}C-TVP101 bound							
		Pool 1		Pool 2		Pool 3		Mean	sd
Mouse	10	72.4	73.1	74.3	72.3	74.1	74.1	73.4	0.9
	100	71.9	72.6	73.2	74.3	74.3	74.7	73.5	1.1
	1000	73.4	73.5	73.0	72.8	74.8	75.2	73.8	1.0
	10000	72.6	75.1	71.2	70.7	72.9	73.4	72.7	1.6
Rat	10	75.7	75.2	78.5	80.0	79.3	80.0	78.1	2.1
	100	75.2	75.2	78.2	78.8	80.7	80.6	78.1	2.5
	1000	77.7	77.6	79.5	79.6	80.8	81.3	79.4	1.5
	10000	77.1	77.1	78.9	78.8	80.4	80.4	78.8	1.5
Dog	10	85.9	85.4	83.8	84.7	88.9	88.9	86.3	2.2
	100	84.7	83.8	84.0	83.6	88.4	88.3	85.5	2.3
	1000	84.8	84.5	84.3	84.9	88.4	88.8	86.0	2.1
	10000	81.7	81.9	81.0	80.9	87.8	87.6	83.5	3.3

Figure 37, from page 15 of Report TVA 108/951876

The *in vitro* binding of ^{14}C-TVP101 to human plasma proteins at various concentrations by ultrafiltration

Target concentration (ng/ml)	% ^{14}C-TVP101 bound									
	1♂		2♂		3♂		4♂		Mean	sd
1	90.5	-	91.6	-	92.3	-	92.6	-	91.8	0.9
10	90.4	92.2	93.7	93.6	93.0	92.0	93.6	93.2	92.7	1.1
100	90.8	90.8	93.5	93.2	92.2	92.5	93.1	93.0	92.4	1.1

Target concentration (ng/ml)	% ^{14}C-TVP101 bound									
	5♀		6♀		7♀		8♀		Mean	sd
1	91.4	-	92.0	-	89.9	-	91.6	-	91.2	0.9
10	91.5	91.3	92.3	92.0	89.7	90.7	91.9	91.7	91.4	0.8
100	90.7	90.7	92.4	92.8	88.7	88.6	91.1	91.2	90.8	1.3

Single determination at 1 ng/ml (see protocol amendment 2)

Figure 38, from page 16 of Report TVA 108/951876

3.3.4 Metabolism

For data in mice, see page 37.

3.3.4.1 [^{14}C]-RASAGILINE MESYLATE BIOTRANSFORMATION IN THE DOG AFTER A SINGLE ORAL ADMINISTRATION

Study: TVA 153/013289

Location: /pk/TVA 153013289.pdf

This study examined the metabolism and excretion of rasagiline in dogs. Three male dogs were administered 1 mg/kg PO. Blood samples were taken at 0, 1, 2, 4 and 8 hours post dose. Rasagiline was extensively metabolized in vivo. At 1 and 2 hours post dose, parent compound was only 4.8 and 1.2% of circulating radioactivity, respectively. The metabolite TVP-136 was only 4.8 and 1.2% of circulating radioactivity at 1 and 2 hours post dose, respectively. 90% of circulating metabolites were not identified in this study. Urine and feces was also examined for rasagiline and metabolites. Radiolabel was primarily excreted in the urine (83%) with a small amount in the feces (5%), mostly within 24 hours. Less than 0.1% of the excreted radioactivity was parent compound. The major metabolites identified in the urine were 3-hydroxy-1(N-propargylamino)-indan (3-OH-PAI) and its glucuronide derivatives. 3-OH-AI and AI were also identified in the urine.

3.3.4.2 PROFILING OF METABOLITES IN RAT URINE FOLLOWING A SINGLE ORAL ADMINISTRATION OF RASAGILINE GIVEN IN TWO DIFFERENT DOSES
Study: 2001-001
Location: /pk/ 2001-001
Rats (3/sex, group M1 and F1) were administered 3 mg/kg radiolabelled rasagiline PO; another group (three males, group M2) received a single dose of 0.1 mg/kg radiolabelled rasagiline PO. Urine was collected for up to 96 hours post dose and analyzed for metabolites.
70-80% of administered radiolabel was excreted within 24 hours in the urine. 78-85% of administered radiolabel was excreted within 48 hours in the urine. There was minimal excretion beyond 48 hours (about 2% of administered radioactivity). Metabolites were profiled using 2D thin layer chromatography. The results in naïve rat urine and in urine treated with glucoronidase are presented below. Spots A-F are highly polar compounds and are probably phase II conjugates. The major unconjugated metabolic products were (in descending order): 3-OH-AI (spot 3), AI (spot 6) and 3-OH-AAI (spot 4). The metabolite profile was similar in males and females at 3 mg/kg in males at 3 and 0.1 mg/kg.

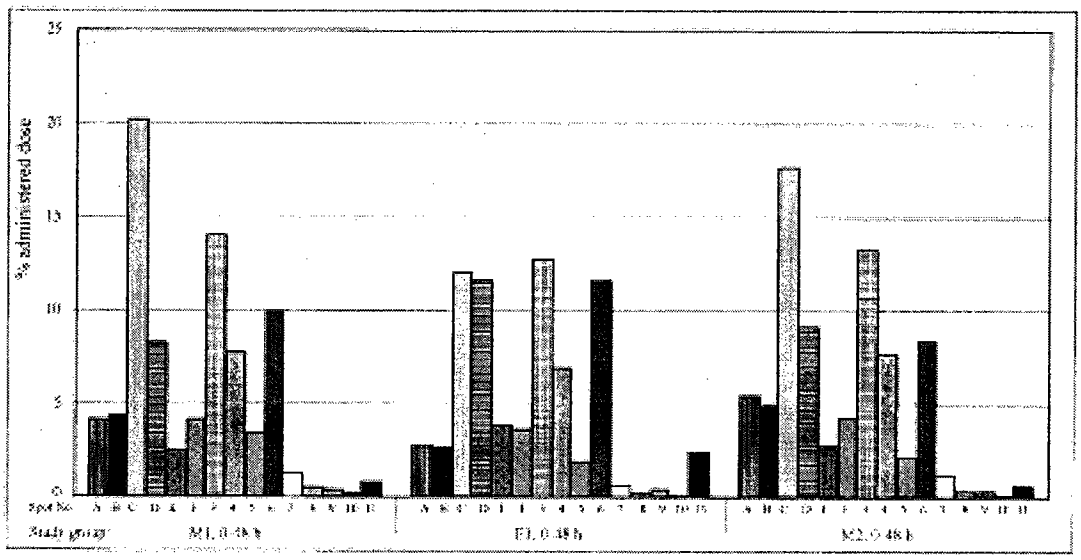

Figure 2. Metabolic profile of Rasagiline in naive rat urine collected 0-48 h post dose
Values shown are means of 3 rats. The following matches with markers were found: Sp 3 = 3-OH-AI (mp), Sp 4 = 3-OH-AAI (mp), Sp 5 = 3-keto-AI, Sp 6 = AI, Sp 7 = 3-keto-AAI, Sp 8 = trans 3-OH-PAI, Sp 10 = 3-keto-PAI, Sp 11 = PAI.

Figure 39, from page 27 of Report 2001-001

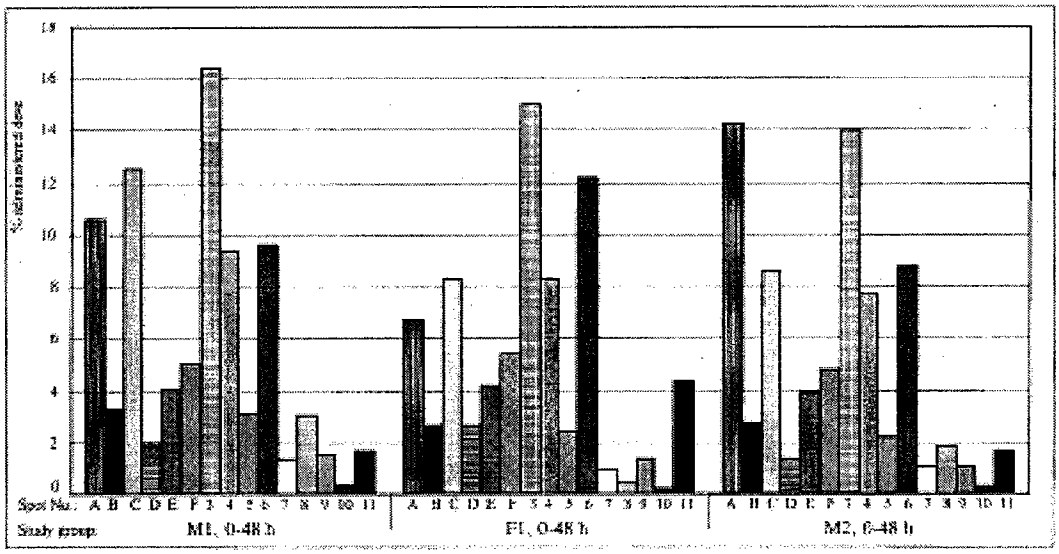

Figure 7. Metabolic profile of Rasagiline after glucuronidase hydrolysis of metabolites in rat urine collected in the 0-48 h post dose period

Figure 40, from page 33 of Report 2001-001

3.3.4.3 ISOLATION AND PARTIAL CHARACTERIZATION OF RAT URINARY RASAGILINE METABOLITES
Study: PK 32
Location: /pk/ PK 32.pdf
3.3.4.4 ^{14}C-PAI METABOLITE IDENTIFICATION IN RAT URINE
Study: TVA124/984688
Location: /pk/TVA 124984688
In study -PK 32, five male Sprague-Dawley rats were administered 4 mg/kg rasagiline for 13 days. On days 10 and 13, four rats were administered radiolabelled rasagiline. Urine samples were analyzed for metabolites from days 10-14 of the study. On day 13, blood samples were obtained from the tail vein at predosing and 1, 4, 8, 12 and 24 hours postdose.
The study was unable to identify plasma metabolites "because the samples were not sufficient enough to perform this research" (page 14 of report). Mean plasma concentration of rasagiline and metabolite combined are presented below. Virtually all of the radioactivity was excreted in the urine. The urine was subjected to multiple extractions with ethyl acetate at various pH's with or without enzyme treatments (beta-glucuronidase and sulfatase). In the urine, the major radiolabel compounds included: parent, 1-aminoindan and N-acetyl-1-aminoindan. The sponsor did not present a quantitative summary of the distribution of radioactivity. The urine was also examined by mass spectrometry (Study TVA 124/984688). Although quantitative results were not obtained, the sponsor proposed a metabolic pathway (see below).

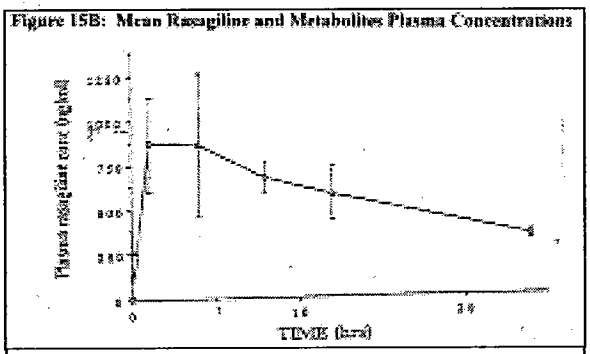

Figure 41, from page 44 of Report /K-32

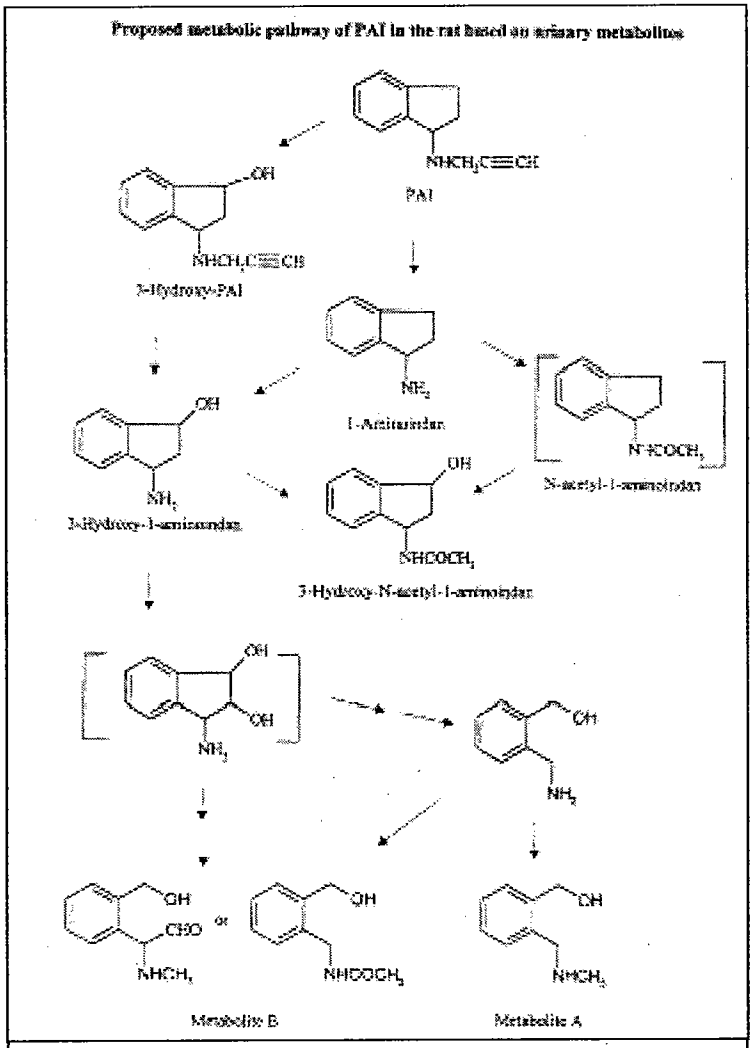

Figure 42, from page 22 of Report TVA 12498688

3.3.4.5 CHARACTERIZATION OF TVP-1012 METABOLISM TESTED IN AN IN VITRO SYSTEM USING HUMAN, DOG AND MOUSE HEPATIC MICROSOMAL PREPARATIONS
Study: -2000-095
Location: /hpbio/hupharm 2000-095.pdf
Rasagiline was incubated with microsomes (1 mg/ml) from various sources (human, dog, rat and mouse) for 60 minutes. The dog was most rapid metabolizer and the human microsomes were the slowest. The dog and rat both formed 3-hydroxy-PAI, but humans and mice did not form this metabolite to any great extent.

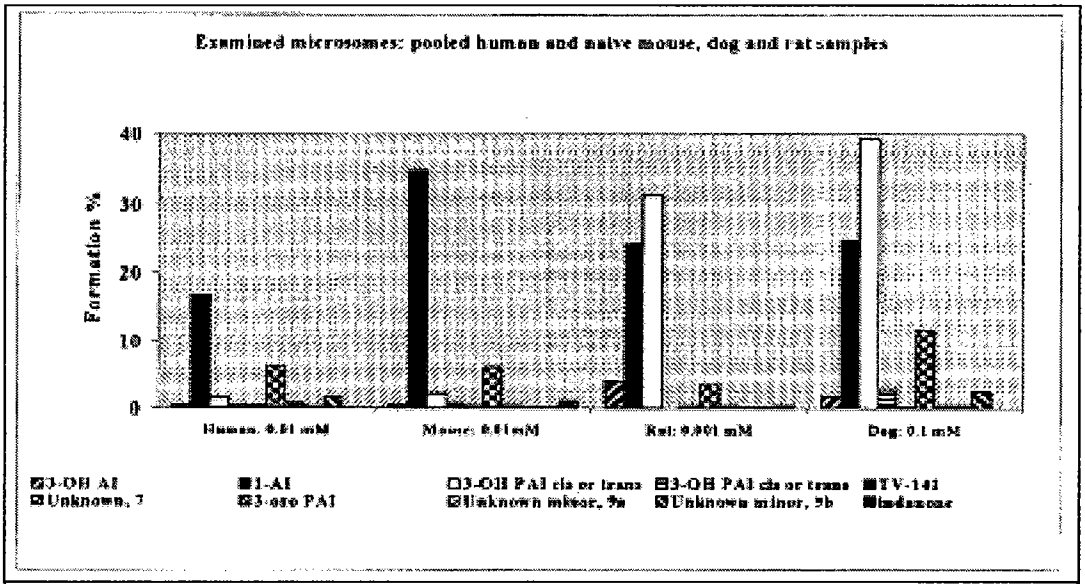

Figure 43, from page 52 of Report 2000-095

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3.3.5 Excretion

For data in mice, see page 37.
For data in rats, see page 44.
For data in dogs, see page 46.

3.3.6 Pharmacokinetic drug interactions

3.3.6.1 COMPARATIVE PROFILING OF LEVODOPA METABOLITES IN RAT PLASMA FOLLOWING SINGLE AND MULTIPLE ORAL ADMINISTRATIONS OF LEVODOPA/CARBIDOPA OR LEVODOPA/CARBIDOPA/RASAGILINE

Study: _000-058

Location: /pk/ 2000-058.pdf

Male rats (8/group) were administered 40/10 mg/kg levodopa/carbidopa with or without 1 mg/kg rasagiline for 1 or 7 days. Levodopa and its metabolites were determine at 0.5, 1, 2, 3, 4, and 8 hours after the last dose of levodopa/carbidopa. Two levodopa metabolites (DOPAC and HVA) had reduced AUC levels, which were attributed to their being products of MAO metabolism. 3-MT is a product of COMT metabolism of dopamine. This suggests that there is increased production of dopamine from levodopa in rats.

Table 6. Pharmacokinetic parameters of levodopa and its metabolites after acid hydrolysis

	Study group: A, single dose without rasagiline					Study group: B, single dose with rasagiline				
	Cmax	Cmax	Tmax	AUC_{0-8h}	AUC_{0-8h}	Cmax	Cmax	Tmax	AUC_{0-8h}	AUC_{0-8h}
	ng/ml	µM	hours	ngxh/ml	µmolxh/l	ng/ml	µM	hours	ngxh/ml	µmolxh/l
DOPAC	844	5.0	0.5	2084	12.4	698	4.2	0.5	1599	9.5
Levodopa	4098	25.8	0.5	12748	64.7	4303	21.9	2.0	14014	71.1
HVA	1289	7.1	2.0	6170	33.9	1433	7.9	0.5	5591	30.7
3-OMD	8506	40.3	4.0	46664	221.2	8485	40.2	4.0	51331	242.3
Dopamine	1046	6.8	1.0	3303	21.6	1069	7.0	1.0	3504	22.9
3-MT	447	2.9	1.0	2916	17.5	635	3.8	4.0	3552	21.3
	Study group: C, multiple doses without rasagiline					Study group: D, multiple doses with rasagiline				
	Cmax	Cmax	Tmax	AUC_{0-8h}	AUC_{0-8h}	Cmax	Cmax	Tmax	AUC_{0-8h}	AUC_{0-8h}
	ng/ml	µM	hours	ngxh/ml	µmolxh/l	ng/ml	µM	hours	ngxh/ml	µmolxh/l
DOPAC	910	5.4	1.0	2629	15.7	269	1.6	1.0	1112	6.6
Levodopa	4655	23.6	1.0	14238	72.2	3042	15.4	1.0	10943	55.5
HVA	1431	7.9	1.0	6775	37.2	709	3.9	1.0	4330	23.8
3-OMD	7057	33.4	8.0	41573	197.0	6018	28.5	8.0	33403	158.3
Dopamine	1307	8.5	1.0	3821	25.0	728	4.8	1.0	3835	25.1
3-MT	516	3.3	4.0	3526	21.1	901	5.4	4.0	5392	32.3

Figure 44, from page 41 of Report 2000-058

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

See page 206.

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ON ORIGINAL

3.4.2 Single-dose toxicity

3.4.2.1 TV-5701182 ACUTE ORAL TOXICITY IN THE MOUSE

Study: Project No. TEV/067/TV

Location: /tox/TEV067TV.pdf

Male and female CD-1 mice were administered rasagiline hydrochloride. The doses were reported as the salt (rather than free base). The doses expressed as free base (salt) are:
Preliminary study: 83 (100), 413 (500), 827 (1000), 1240 (1500), 1653 (2000) mg/kg
Main study males: 66 (80), 132 (160), 264 (320) and 529 (640) mg/kg
Main study females: 129 (156), 207 (250), 331 (400), 529 (640), 846 (1024) and 1354 (1638) mg/kg.
Mortality results are presented below. No clinical signs were observed at 207 mg/kg and below. Ataxia and decreased motor activity were observed in all rats at 264 mg/kg and above. The sponsor estimated that the LD50 (95% confidence intervals) were 485 mg/kg (345-681) and 364 mg/kg (301-439) for males and females, respectively.

Mortality in groups of male and female mice given a single oral dose of TV-5701182 in double-distilled water at a volume-dosage of 10 ml/kg

Preliminary Study

Dose level (mg/kg)	Mortality		
	Males	Females	Combined
100	0/2	0/2	0/4
500	2/2	0/2	2/4
1000	2/2	1/2	3/4
1500	2/2	2/2	4/4
2000	-	2/2	-

Main Study

Dose level (mg/kg)	Mortality
	Males
80	0/5
160	0/5
320	1/5
640	5/5

Dose level (mg/kg)	Mortality
	Females
156	0/5
250	1/5
400	5/5
640	5/5
1024	5/5
1638	5/5

Figure 45, from page 19 of Report TEV067TV

3.4.2.2 TVP 101 AND TVP 1012 COMPARATIVE ORAL TOXICITY TO THE RAT
Study: 920722D/TVA 69/AC
Location: /tox/920722D TVA 69AC.pdf
Sprague Dawley rats (5/swex/dose) were administered rasagiline as either the hydrochloride (TVP-101) or mesylate (TVP-1012) salt. Doses were expressed as the salt form. Mortality was similar with the two salt forms. No significant differences were observed in clinical signs (lethargy, decreased respiratory rate) between the two groups. Deaths occurred over a period of three days.

Mortality and LD50 (in mg/kg) in rats administered two salt forms of rasagiline

	TVP-101 (hydrochloride)			TVP-1012 (mesylate)		
Salt dose	160	250	400	250	400	640
Base dose	133	208	332	160	256	410
Males	1/5	3/5	4/5	0/5	3/5	5/5
LD50	201 (148-269)			246 (192-314)		
Females	0/5	0/5	5/5	0/5	2/5	5/5
LD50	266 (193-396)			269 (211-344)		
Combined	1/10	3/10	9/10	0/10	5/10	10/10
LD50	227 (183-295)			256 (216-306)		

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ON ORIGINAL

3.4.2.3 TVP-5701182 MAXIMUM TOLERATED DOSE STUDY IN BEAGLE DOGS BY THE ORAL ROUTE

Study: TEV/058/TV

Location: /tox/TEV058TV.pdf

Three groups of dogs (1/sex/dose) were administered single doses of rasagiline hydrochloride 0.85, 3.4, 17, 25.5, 51 or 102 mg/kg. The equivalent doses of free base are 0.7, 2.8, 14, 21, 42 and 84 mg/kg, respectively. Sufficient time was allowed between doses to ensure full recovery (21 days between doses).

Both dogs administered 84 mg/kg (free base) died 2-3 days post dosing. Clinical signs included vomiting (2 dogs), diarrhea (1 dog), blood in feces and mouth (1 dog) and decreased food consumption (2 dogs).

At 42 mg/kg (free base), dogs had diarrhea on Day 2. No other significant adverse effects were noted at this dose.

No significant effects were observed at 21 mg/kg (free base) or below.

3.4.3 Repeat-dose toxicity

3.4.3.1 TOXICITY TO RATS BY REPEATED ORAL ADMINISTRATION FOR 26 WEEKS WITH A 13 WEEK RECOVERY PERIOD

Key study findings:
1. Decreased body weight (final body weight 90% or less of control body weights) were observed at 5.1 mg/kg in males and 17 mg/kg in females.
2. Salivation was observed at 5.1 and 17 mg/kg.
3. Aggressive behavior and subdues behavior were observed at 17 mg/kg, mostly early in the study.
4. Effects were observed on the liver. Increased adjusted liver weight was observed at 17 mg/kg. Centrilobular hypertrophy was also observed at 17 mg/kg.
5. Thyroid follicular hypertrophy was observed at 17 mg/kg.

Study no.: TVA 133/993217
Location: /tox/ TVA 133993217.pdf
Conducting laboratory and location: —

Date of study initiation: March 17, 1993
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 255493203 — pure

Methods

Doses: 0, 0.85, 5.1, 17 mg/kg/day
Species/strain: Rat, – .CD BR
Number/sex/group or time point (main study): 20 rats/sex/dose
Route, formulation, volume, and infusion rate: Gavage, water vehicle, 10 ml/kg
Satellite groups used for recovery: 5/sex (control and high dose)
Satellite groups used for toxicokinetics: 5/sex/dose (treated only)
Age: 6 weeks
Weight (nonrodents only):
Unique study design or methodology (if any):

Observation times and results

Mortality:
17 mg/kg male #68 was sacrificed due to injuries resulting from fighting in week 2.
17 mg/kg female #161 died due to malignant lymphoma in week 13.

Clinical signs: 1X/day
17 mg/kg- aggressive behavior and subdued behavior; this was observed mostly early in the study.
5.1 mg/kg and above- salivation and brown perioral staining throughout the study
0.85 mg/kg- no clinical signs were observed

Body weights: 1X/week
Decreased body weight observed at 0.85 mg/kg and above in males and 5.1 mg/kg and above in females

Week 26 Body Weights as Percent of Controls

	0.85 mg/kg	5.1 mg/kg	17 mg/kg
Males	91%	84%	78%
Females	101%	93%	90%

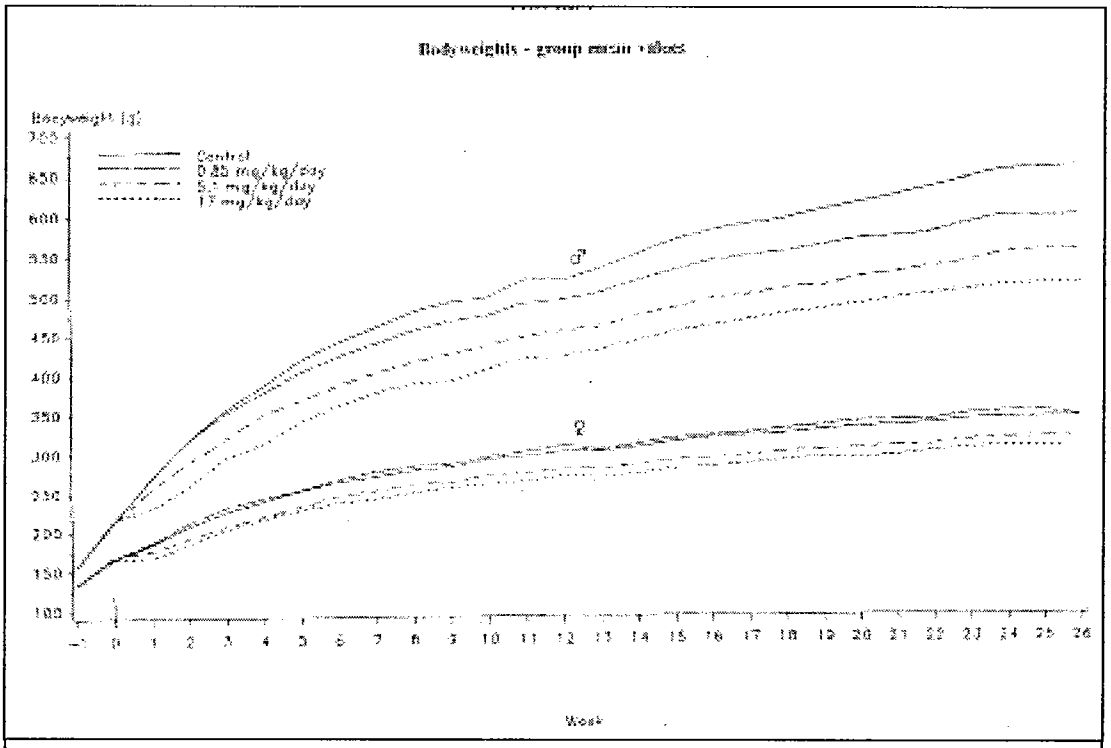

Figure 46, from page 38 of Report TVA 76930540

Food consumption: 1X/week
Reduced food consumption was observed at 0.85 (males only), 5.1 and 17 mg/kg in both males and females.

Cumulative Food Consumption in g/rat (% of control)

	0 mg/kg	0.85 mg/kg	5.1 mg/kg	17 mg/kg
Males	5,736	**5,194 (91%)**	**4,625 (81%)**	**3,650 (81%)**
Females	4,009	4,025 (100%)	**3497 (87%)**	**2,633 (91%)**

Values in **Bold** significantly different from controls

Ophthalmoscopy: Pre, Weeks 13, 26 (control and 17 mg/kg only)
No effects

EKG: Not done

Hematology: Weeks 13, 26
No effects

Clinical chemistry: Weeks 13, 26
No significant effects

Urinalysis: Weeks 13, 26
No significant effects

Gross pathology:
No significant effects.

Organ weights:
Increased adjusted liver weight at 17 mg/kg.

Body Weight Adjusted Liver Weights (in g)

	0 mg/kg	0.85 mg/kg	5.1 mg/kg	17 mg/kg
Males	20.4	22.3	22.1	**25.0**
Females	12.5	12.0	12.4	**13.7**

Values in **Bold** significantly different from controls

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ( )
Control and High dose only, except liver, thyroid, urinary bladder and gross lesions at low and mid dose.

Incidence of hepatic centrilobular hypertrophy

	0 mg/kg	0.85 mg/kg	5.1 mg/kg	17 mg/kg
Males	2/20	3/20	3/20	19/19
Females	0/20	0/20	3/20	13/19

Incidence of Thyroid follicular hypertrophy

	0 mg/kg	0.85 mg/kg	5.1 mg/kg	17 mg/kg
Males	2/20	0/20	2/20	5/19
Females	1/20	1/20	0/20	7/19

Toxicokinetics: Days 1, 90, 181; 0.25 and 6 hours post dose

Plasma concentration of Rasagiline (ng/ml) at various times after dosing

Dose mg/kg	Sex	Day 1		Day 90		Day 181	
		0.25 hr	6 hr	0.25 hr	6 hr	0.25 hr	6 hr
0.85	M	115.34	2.50	80.36	6.68	128.68	8.64
	F	53.00	15.4	105.28	4.76	144.44	5.26
5.1	M	190.90	9.92	602.40	50.12	337.60	28.64
	F	351.36	17.88	601.00	54.56	1147.60	50.20
17	M	1058.60	82.80	1975.40	142	2278.80	233.40
	F	1402.40	136.72	2043.80	208.00	3464.40	243.80

Plasma concentration of AI (ng/ml) at various times after dosing

Dose mg/kg	Sex	Day 1		Day 90		Day 181	
		0.25 hr	6 hr	0.25 hr	6 hr	0.25 hr	6 hr
0.85	M	16.56	12.32	31.86	11.02	32.68	10.44
	F	35.86	14.70	58.12	21.16	55.88	23.22
5.1	M	106.14	49.64	138.00	49.36	70.80	26.94
	F	134.30	89.70	166.84	142.12	236.20	130.20
17	M	275.00	144.72	391.20	183.20	405.60	167.00
	F	339.20	237.44	510.20	535.20	602.80	423.60

Other:
Recovery animals had increased weight gain during the recovery period.
No significant histological alterations were noted in recovery animals.

3.4.3.2 4 WEEK ORAL (GAVAGE) COMBINATION DOSE RANGE FINDING STUDY WITH TVP-1012 (RASAGILINE MESYLATE), LEVODOPA AND CARBIDOPA IN RATS

Key study findings:

1. Rats did not tolerate the combination of 3 mg/kg rasagiline and 80/20 levodopa/ carbidopa. Increased mortality and decreased combination, especially in males. Deaths occurred after the dose was lowered to 2 mg/kg. No specific target organs were identified.
2. The 0.3 mg/kg dose had no effect on levodopa PK parameters, but 2 mg/kg lowered the Cmax and AUC values by 54% and 57%, respectively.
3. Levodopa/carbidopa lowered the rasagiline Cmax and AUC values by 73% and 15%, respectively.

Study no.: TVA 133/993217
Location: /tox/TVA133993217 and /tox/TVA 174013969
Conducting laboratory and location:

Date of study initiation: May 25, 1999
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: CN-255400199
Methods

Species/strain: Rat, CD
Route, formulation, volume, and infusion rate: oral gavage, 10 ml/kg
Age: 39-43 days
Unique study design: rasagiline was coadministered with levodopa/carbidopa

Group	Treatment	Dosage (mg/kg/day) Base form (TVP-1012)	Dosage (mg/kg/day)# Salt form (TVP-1012)	Dosage (mg/kg/day)§ Levodopa/ Carbidopa	Number of animals			
					Main study		Satellite study‡	
					Male	Female	Male	Female
1	Control	0	0	0	10	10	-	-
2	TVP-1012 (Rasagiline Mesylate)	3/0.2/0*	4.6/0.3/0	0	10	10	12	12
3	Levodopa/Carbidopa†	0	0	80/20	10	10	12	12
4	TVP-1012 (Rasagiline Mesylate) + Levodopa/Carbidopa*	0.3	0.47	80/20	10	10	12	12
5	TVP-1012 (Rasagiline Mesylate) + Levodopa/Carbidopa*	2.0	1.86	80/20	10	10	-	-
6	TVP-1012 (Rasagiline Mesylate) + Levodopa/Carbidopa*	3/0.2/0*	4.6/0.3/0	80/20	10	10	12	12

* Dosages (mg/kg/day) expressed in terms of the mesylate salt (as supplied)
† Ratio of Levodopa to Carbidopa was 4 : 1. The specified dosages of TVP-1012 for Groups 4 to 6 were in combination with Levodopa/Carbidopa at a constant dosage of 80/20 mg/kg/day.
§ The Carbidopa was supplied as a monohydrate salt and dosages are expressed in terms of the anhydrous form. The conversion factor monohydrate : anhydrate was 1.072.
‡ Satellite animals used for Toxicokinetic sampling only.
* Dosage of TVP-1012 reduced from 3.0 mg/kg/day to 2.0 mg/kg/day from Day 12 of treatment.

Figure 47, from page 15 of Report TVA 134993925

Observation times and results

Mortality:
These deaths occurred after the high dose of rasagiline was reduced from 3 to 2 mg/kg (day 12) due to poor body weight gain

Group /sex	Animal No.	Mode of death	Day of death	Significant *ante-mortem* findings
5M	49	Killed *in extremis*	27	Underactive, piloerection, hunched posture, deep respiration.
6M	51	Killed *in extremis*	27	Thin, irritable, underactive, piloerection, ataxia, limited use of forelimbs, hunched posture, deep and laboured respiration.
	52	Killed *in extremis*	31	Thin, piloerection, ataxia
	55	Died	27	None
	57	Killed *in extremis*	31	Salivation, piloerection, dilated pupils, ataxia
	58	Killed *in extremis*	30	Salivation, piloerection, convulsion, prostrate posture
	59	Killed *in extremis*	24	Underactive, piloerection, ataxia, irregular respiration
6F	117	Killed *in extremis*	32	Thin, underactive, piloerection, pallor, limited use of forelimbs, irregular and slow respiration
	120	Killed *in extremis*	32	Thin, underactive, piloerection, pallor, dull eyes, limited use of forelimbs, slow respiration

Figure 48, from page 29 of Report TVA 134993925h

No specific target organ histopathological changes were observed.

Clinical signs: 1X/day; also 1X/week detailed examination

Group	:	1	2	3	4	5	6
Compound	:	Control	TVP-1012	Levodopa/Carbiodpa	TVP-1012 + Levodopa/Carbiodpa		
Dosage (mg/kg/day)	:	0	3.0/2.0	80/20	0.3 + 80/20	1.0 + 80/20	3.0/2.0 + 80/20

Sign	Sex:	Male						Female					
	Group:	1	2	3	4	5	6	1	2	3	4	5	6
	Group size:	10	10	10	10	10	10	10	10	10	10	10	10
Piloerection		0	1	10	10	10	10	0	0	10	10	10	10
Irritable		0	0	0	0	0	0	0	2	0	2	6	10
Prostrate		0	0	6	7	7	4	0	0	1	0	2	2
Salivation		0	0	0	0	5	6	0	0	0	0	0	6
Urine staining (wet perigenital)		0	0	0	0	3	1	0	0	0	0	0	0
Hunched		0	0	0	0	1	0	0	0	0	0	0	0
Underactive		0	0	0	0	0	1	0	0	0	0	0	0
Ataxia		0	0	0	0	0	1	0	0	0	0	0	0

Figure 49, from page 40 of Report TVA 134/993925

Body weights:

Effect of Treatment on Final Body Weight in grams (% of control)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Male	354	328 (93%)	355 (100%)	347 (98%)	330 (93%)	283 (80%)
Female	233	216 (93%)	233 (100%)	223 (96%)	223 (96%)	216 (93%)

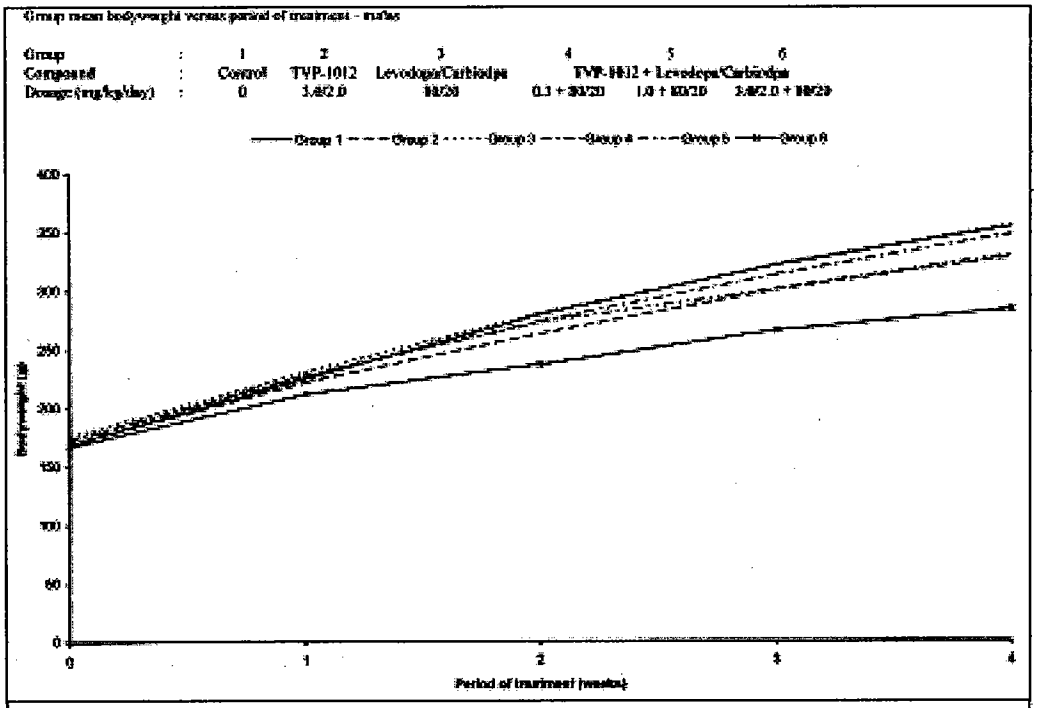

Figure 50, from page 38 of Report TVA 134/993925

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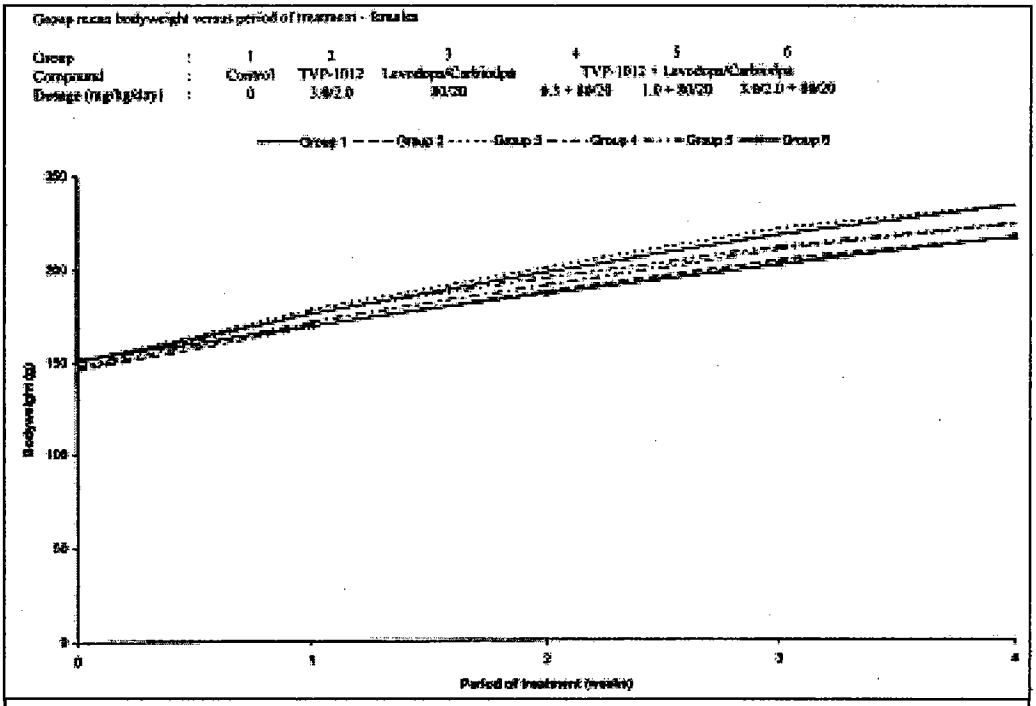

Figure 51, from page 39 of Report TVA 134/993925

Food consumption: 1X/week
Group 6 males had decreased food consumption (86% of control).
Group 2 males had decreased food consumption (89% of control).

Ophthalmoscopy: Not done

EKG: Not done

Hematology: Week 5
No significant effects

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ON ORIGINAL

Clinical chemistry: Week 5

Male changes in clinical chemistry

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Urea (umol/l)	3.90	4.06	4.37	3.90	**5.40**	**7.23**
Glucose (mmol/l)	4.57	**6.25**	**6.78**	**6.22**	**6.79**	**7.84**
ALT (u/l)	43	31	24	25	22	24
AST (u/l)	74	71	65	68	81	**91**
Albumin (g/l)	35	34	35	37	34	33

Values in **Bold** significantly different from control ($p<0.05$)

Female changes in clinical chemistry

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Urea (umol/l)	5.08	5.03	4.60	5.32	**6.17**	**6.88**
Glucose (mmol/l)	5.85	5.85	6.31	7.23	**6.53**	**6.91**
ALT (u/l)	34	31	25	22	23	**73**
AST (u/l)	68	67	69	72	71	**322**
Albumin (g/l)	42	**39**	39	**38**	**38**	**34**

Values in **Bold** significantly different from control ($p<0.05$)

Urinalysis: Week 5

Male changes in urinalysis

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Volume (ml)	19.6	**12.9**	14.3	22.4	**12.5**	**2.6**
Specific Gravity (g/l)	1017	1020	1020	1012	1020	**1051**

Values in **Bold** significantly different from control ($p<0.05$)

Female changes in urinalysis

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Volume (ml)	11.8	12.0	18.0	18.1	10.6	6.3
Specific Gravity (g/l)	1021	1018	1013	1015	1024	**1035**

Values in **Bold** significantly different from control ($p<0.05$)

Gross pathology:
No effects

Organ weights (specify organs weighed if not in histopath table):

Male changes in relative organ weights (expressed as %body weight)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Spleen	0.192	0.197	0.172	0.200	0.169	**0.147**
Thymus	0.141	0.133	0.136	0.162	0.136	**0.117**

Values in **Bold** significantly different from control ($p<0.05$)

Female changes in relative organ weights (expressed as %body weight)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Spleen	0.225	0.224	0.217	0.210	0.206	**0.182**
Thymus	0.201	0.219	0.228	0.179	0.196	**0.127**

Values in **Bold** significantly different from control ($p<0.05$)

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
Histological changes in decedent animals were apoptotic changes in the stomach, intestines, thymus, spleen, liver, pancreas and prostate associated with poor clinical condition.

No specific histological changes were observed in rats terminated at the end of the study.

Toxicokinetics: Rats were sampled at 0, 0.5, 1, 2, 4, and 6 hours post-dose (4/sex/timepoint)

Pharmacokinetic parameters of PAI on Day 30 of treatment following daily oral administration of rasagiline mesylate to rats with or without co-administration of levodopa/carbidopa at a dose level of 80/20 mg/kg/day

Males

Dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
3.0/2.0[a,b]	127.0	0.5	190.1	-	c	-
0.3	4.2	2	21.8	-	c	-
3.0/2.0[a]	43.0	0.5	171.0	-	c	-

Females

Dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
3.0/2.0[a,b]	168.7	0.5	169.6	-	c	-
0.3	6.5	0.5	26.8	-	c	-
3.0/2.0[a]	35.7	4	135.4	-	c	-

a Dose reduced from 3.0 mg/kg/day to 2.0 mg/kg/day from Day 12 of treatment
b No administration of levodopa and carbidopa
c Terminal rate constant could not be estimated adequately

Figure 52, from page 20 of Report TVA 174/013969

Pharmacokinetic parameters of AI on Day 30 of treatment following daily oral administration of rasagiline mesylate to rats with or without co-administration of levodopa/carbidopa at a dose level of 80/20 mg/kg/day

Males

Dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
3.0/2.0[a,b]	79.5	0.5	300.2	-	c	-
0.3	6.9	6	29.7	-	c	-
3.0/2.0[a]	54.0	4	208.5	-	c	-

Females

Dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
3.0/2.0[a,b]	132.3	0.5	434.5	-	c	-
0.3	8.9	6	39.8	-	c	-
3.0/2.0[a]	51.3	4	198.4	-	c	-

a Dose reduced from 3.0 mg/kg/day to 2.0 mg/kg/day from Day 12 of treatment
b No administration of levodopa and carbidopa
c Terminal rate constant could not be estimated adequately

Figure 53, from page 21 of Report TVA174/013969

Pharmacokinetic parameters of levodopa on Day 30 of treatment following daily oral administration of levodopa/carbidopa to rats at a dose level of 80/20 mg/kg/day with or without co-administration of rasagiline mesylate

Males

Rasagiline dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
0	8592.4	4	37532	-	b	-
0.3	9444.6	4	40126	-	b	-
3.0/2.0*	2539.1	4	13010	-	b	-

Females

Rasagiline dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
0	6253.1	1	27246	-	b	-
0.3	5901.7	4	26383	-	b	-
3.0/2.0*	3848.1	0.5	13334	-	b	-

* Dose reduced from 3.0 mg/kg/day to 2.0 mg/kg/day from Day 12 of treatment
b Terminal rate constant could not be estimated adequately

Figure 54, from page 22 of Report TVA 174/013969

Pharmacokinetic parameters of carbidopa on Day 30 of treatment following daily oral administration of levodopa/carbidopa to rats at a dose level of 80/20 mg/kg/day with or without co-administration of rasagiline mesylate

Males

Rasagiline dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
0	221.3	4	1145	-	b	-
0.3	303.4	0.5	1488	-	b	-
3.0/2.0*	248.1	0.5	906	-	b	-

Females

Rasagiline dose level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_t (ng.h/ml)	AUC (ng.h/ml)	k ($hours^{-1}$)	t½ (hours)
0	251.5	2	968	-	b	-
0.3	191.3	6	964	-	b	-
3.0/2.0*	194.5	0.5	789	-	b	-

* Dose reduced from 3.0 mg/kg/day to 2.0 mg/kg/day from Day 12 of treatment
b Terminal rate constant could not be estimated adequately

Figure 55, from page 23 of Report TVA 174/013969

Other:

3.4.3.3 13 WEEK ORAL (GAVAGE) COMBINATION TOXICITY STUDY WITH TVP-1012 (RASAGILINE MESYLATE), LEVODOPA AND CARBIDOPA IN RATS

Key study findings

1. Combination of 1 mg/kg rasagiline with 80/20 mg/kg levodopa/carbidopa caused increased mortality and body weight changes.
2. Rats tolerated 1mg/kg rasagiline alone or 80/20 mg/kg levodopa/carbidopa alone with no significant effects.
3. Rasagiline had no significant effect on levodopa levels, but levodopa decreased 1 mg/kg rasagiline Cmax and AUC by 72% and 28%, respectively.

Study no.: TVA 162/013506
Location: /tox/TVA162013506
Conducting laboratory and location: [redacted]

Date of study initiation: March 27, 2001
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: CN-255400100

Methods

Doses: See table below
Species/strain: Rats, CD strain
Number/sex/group or time point (main study): See table below
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: See table below
Age: 6 weeks
Unique study design or methodology (if any):

Group No.	Treatment	Dosage (mg/kg/day)		Number of animals			
		Base form Rasagiline Mesylate (TVP-1012)	Levodopa/ Carbidopa	Main study Male	Main study Female	Satellite study Male	Satellite study Female
1MF	Control (aqueous acidified 0.5% methylcellulose solution)	0	0	10	10	6	6
2MF	Levodopa/Carbidopa	0	80/20	10	10	9	9
5MF	Rasagiline Mesylate (TVP-1012)	1.0	0	10	10	9	9
4MF	Rasagiline Mesylate (TVP-1012) + Levodopa/Carbidopa	0.1	80/20	10	10	9	9
3M	Rasagiline Mesylate (TVP-1012) + Levodopa/Carbidopa	0.25	80/20	10	0	0	0
6MF	Rasagiline Mesylate (TVP-1012) + Levodopa/Carbidopa	0.5	80/20	10	10	9	9
7MF	Rasagiline Mesylate (TVP-1012) + Levodopa/Carbidopa	1.0	80/20	10	10	9	9

Figure 56, from page 15 of Report TVA 162/013506

Observation times and results

Mortality: 1X/day

Group Sex	Animal No.	Mode of death	Week of death	Significant non-narrative signs and necropsy findings
7M	63	Died	8	Signs - no significant signs Necropsy - clotted blood in the cranium, firm caecal contents.
	65	Died	9	Signs – no significant signs Necropsy – skin, muscle and bone on nose partially cannibalised.
	66	Killed in extremis	9	Signs - piloerection, underactivity, hunched posture. Animal killed due to its poor condition; no blood samples taken. Necropsy – oedematous adipose tissue, abdominal distension, congested liver, depressed areas on glandular surface of stomach
	67	Killed in extremis	9	Signs - both eyes cannibalised; red staining on the head. Animal killed due to its poor condition; no blood samples taken. Necropsy - eyes, right Harderian gland and right optic nerve cannibalised, skin, musculature and peri-orbital bone partially cannibalised.
	69	Died	10	Signs – no significant signs Necropsy – no significant findings. Head partially cannibalised.
7F	128	Died	10	Signs – no significant signs. Necropsy – no significant findings. Extensive cannibalisation.

Figure 57, from page 30 of Report TVA 162/013506

Clinical signs: 1X/day

Piloerection was observed in rats treated with levodopa/carbidopa with or without rasagiline. Onset was earlier in rats treated with the combination (week 8 for all combination groups) than in the group treated without rasagiline (week 11). There was no apparent dose response relationship with rasagiline.

Body weights: 1X/week

Final Body Weights in Grams (% control)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Males	512	471 (92)	488 (95)	482 (94)	477 (93)	439 (86)	412 (80)
Females	298	295 (99)	283 (95)	287 (96)	---	273 (92)	281 (94)

--- No female group 5

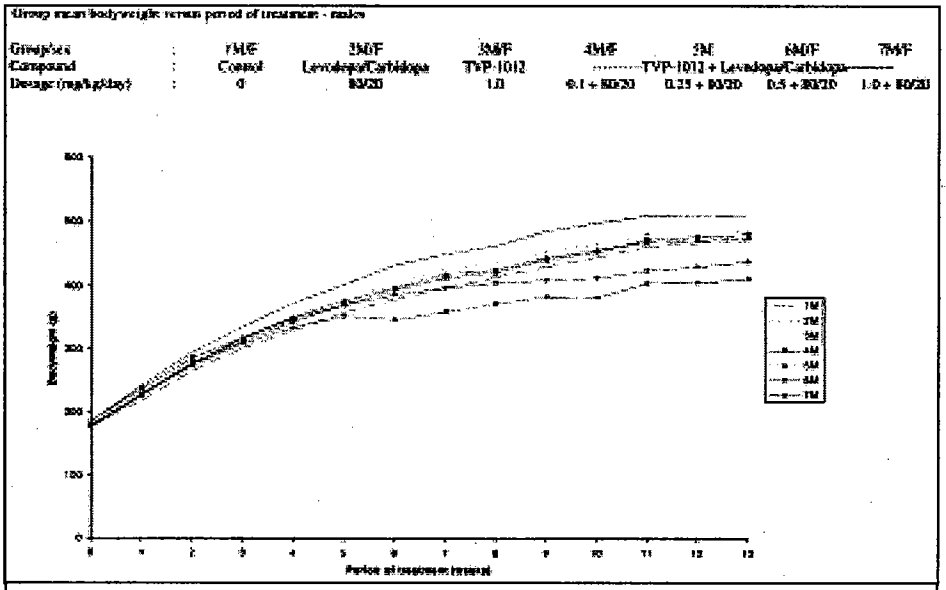

Figure 58, from page 42 of Report TVA 162/013506

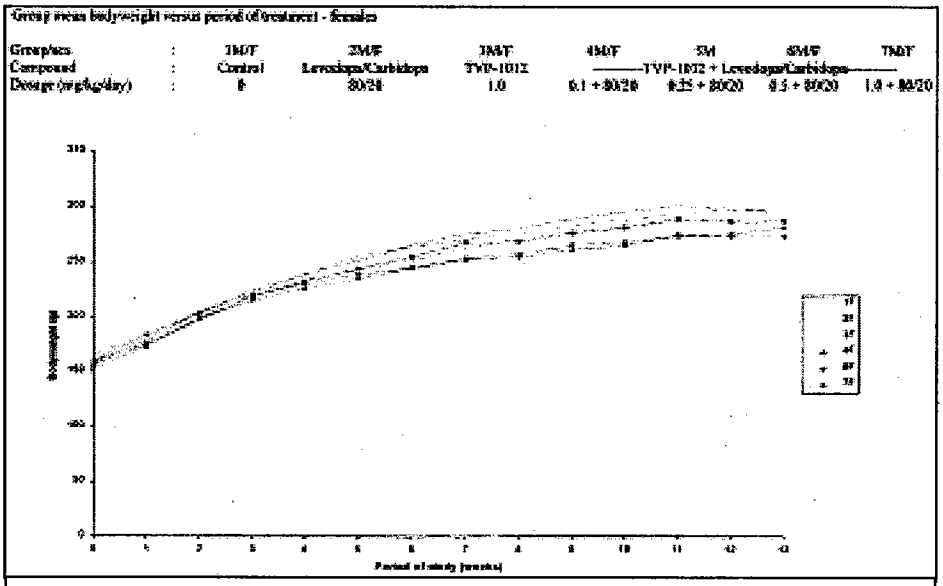

Figure 59, from page 43 of Report TVA 162/013506

Food consumption: 1X/week
No effects

Ophthalmoscopy: Pre, Week 13
No effects

EKG: Not done

Hematology: Week 13
No significant effects

Clinical chemistry: Week 13
No significant effects

Urinalysis: Week 13
No significant effects.

Gross pathology:
No significant effects

Organ weights (specify organs weighed if not in histopath table):
No significant effects

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
No significant effects

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Toxicokinetics: Rasagiline had no significant effect on levodopa levels, but levodopa decreased rasagiline Cmax and AUC.

Maximum plasma concentration and AUC for PAI on Day 30

Group	Dosage (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
3	1.0a	48.5	57.4	122.5	83.8
4	0.1	b	3.1	c	c
6	0.5	7.2	8.5	42.4	43.8
7	1.0	14.9	14.2	75.6	69.2

a Levodopa/carbidopa were not administered to this group
b Maximum mean plasma concentration was below the limit of quantification
c Insufficient data to calculate AUC_t

Figure 60, from page 33 of Report TVA 162013506

Maximum plasma concentration and AUC for aminoindan on Day 30

Group	Dosage (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
3	1.0a	41.6	55.1	167.3	205.4
4	0.1	2.4	3.2	b	b
6	0.5	8.5	13.7	57.1	88.5
7	1.0	16.3	22.3	113.8	153.8

a Levodopa/carbidopa were not administered to this group
b Insufficient data to calculate AUC_t

Figure 61, from page 33 of Report TAV 162013506

Maximum plasma concentration and AUC for Levodopa on Day 30

Group	Dosage of TVP-1012 (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
2	0	5388.5	4401.9	23828	17318
4	0.1	6838.7	4509.1	29215	17681
6	0.5	4587.8	4125.8	27993	24834
7	1.0	4081.6	3033.8	20105	17641

Figure 62, from page 34 of Report TVA 162013506

Maximum plasma concentration and AUC for Carbidopa on Day 30

Group	Dosage of TVP-1012 (mg/kg/day)	C_{max} (ng/ml)		AUC_t (ng.h/ml)	
		Males	Females	Males	Females
2	0	82.7	131.5	344	663
4	0.1	83.8	214.8	373	632
6	0.5	83.1	117.9	475	731
7	1.0	57.4	150.7	281	721

Figure 63, from page 34 of Report TVA 162013506

Other:

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3.4.3.4 SUBCHRONIC ORAL TOXICITY STUDY IN MICE WITH TVP-1012

Key study findings:
1. Some body weight effects were observed at 45 mg/kg and above in males and 60 mg/kg and above in females. These effects were less than 10% of the body weight and the significance is uncertain.
2. Liver hypertrophy (as indicated by increased relative liver weight and hepatocellular enlargement) was observed 15 mg/kg and above in males and 60 mg/kg and above in females.
3. No other effects on hematology, urinalysis or pathology were observed. No clinical chemistry studies were done.

Study no.: — 2695-106
Location: /tox — 2695-106.pdf
Conducting laboratory and location: —
Date of study initiation: April 18, 1996
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 255495223

Methods

Doses: 0, 5, 15, 45, 60, 100 mg/kg
Species/strain: Mouse, — .CD-1(ICR)BR
Number/sex/group or time point (main study): 10/sex/dose
Route, formulation, volume, and infusion rate: Oral gavage
Satellite groups used for toxicokinetics: 99/sex (5, 45 and 60 mg/kg only)
Age: 7 weeks
Unique study design or methodology (if any):

Observation times and results

Mortality:
0 mg/kg- 2 males died (Day 57, 81)
100 mg/kg- 1 female (A60398) found dead on Day 7

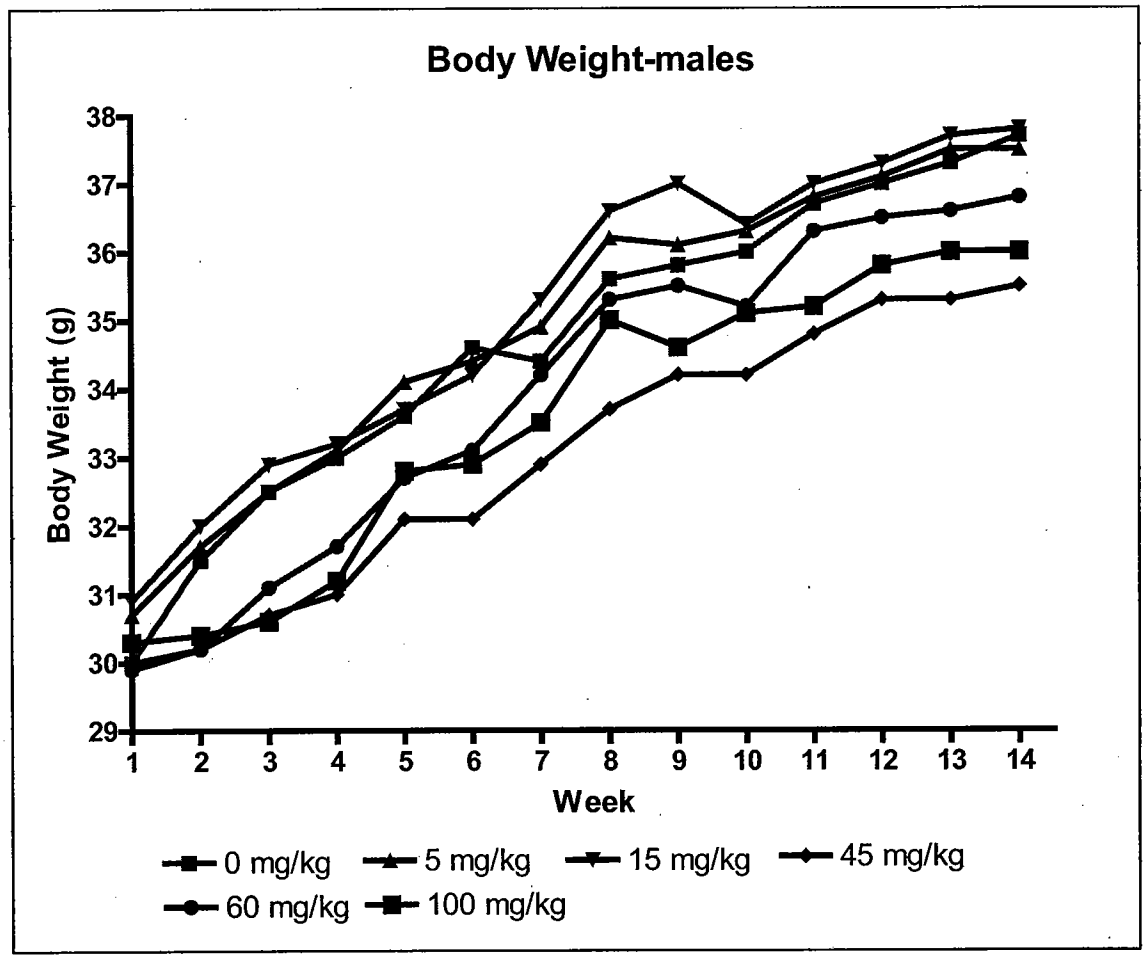
Clinical signs: 1X/day
100 mg/kg- 1 female had tremors (found dead on Day 7)
No other significant increase in clinical signs.

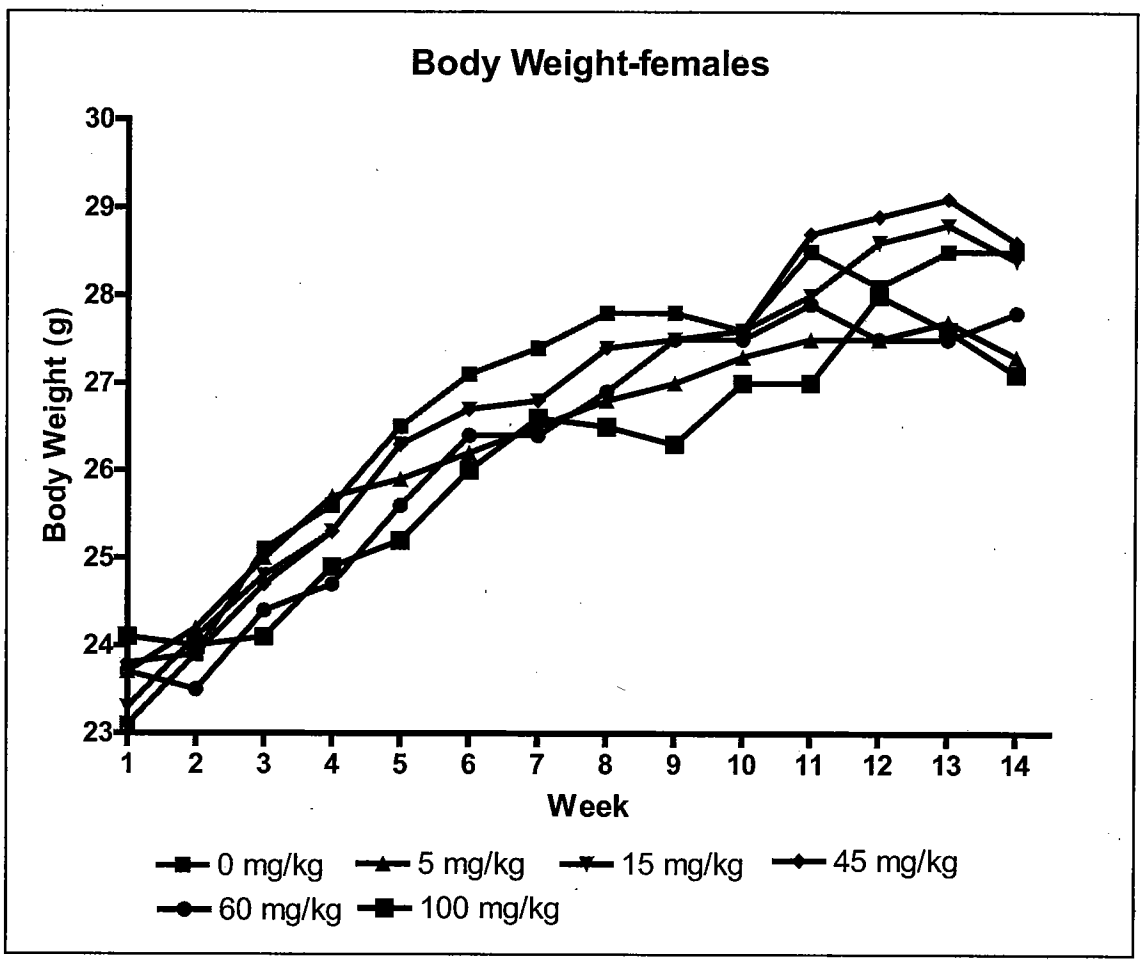
Body weights: 1X/week
In general, body weights of male mice at 45 mg/kg and above were lower than controls, but differences were less than 10%; body weights of female mice at 60 and 100 mg/kg were lower than controls, although differences were less than 10%.

Cumulative Body Weight Changes in Grams (Week 14 BW - Week 1 BW)

	0 mg/kg	5 mg/kg	15 mg/kg	45 mg/kg	60 mg/kg	100 mg/kg
Males	7.5	6.8	6.9	5.6	6.9	5.7
Females	5.3	**3.6**	5.1	4.8	4.2	**3.1**

Values in **Bold** significantly different from controls.





Food consumption: 1X/week
No effects

Ophthalmoscopy: Week 13
No effects

EKG: Not done

Hematology: Week 14
No effects

Clinical chemistry: Not done

Urinalysis: Week 14
No effects

Gross pathology:
No effects

Organ weights:
Increased liver weight was observed at 45 mg/kg and above in both males and females.

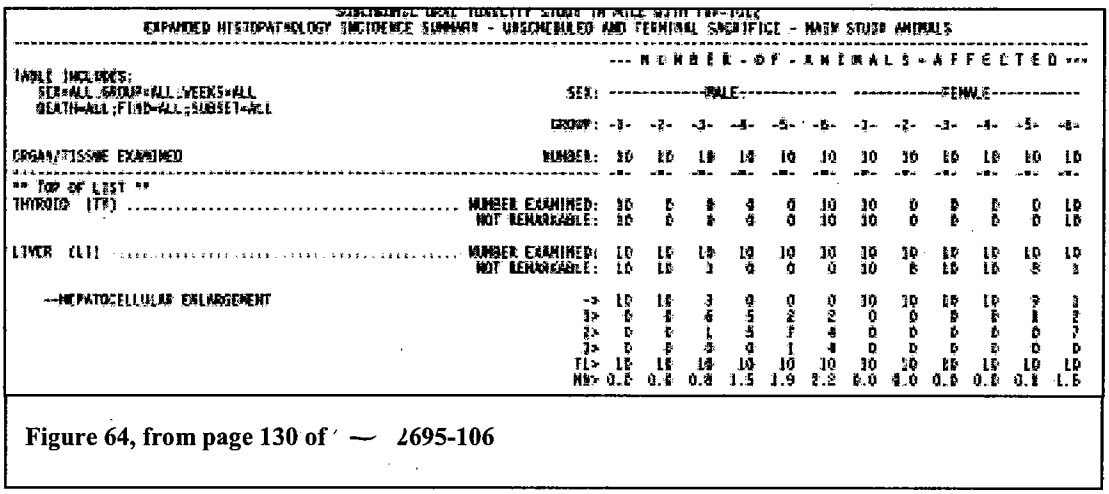
Relative organ weights (%body weight)-Males

Organ	0 mg/kg	5 mg/kg	15 mg/kg	45 mg/kg	60 mg/kg	100 mg/kg
Liver	4.41	4.42	4.61	**5.16**	**5.24**	**5.75**
Testes	1.50	1.43	1.40	1.46	1.36	1.19
Prostate	0.292	0.256	0.221	0.222	0.213	0.228
Seminal vesicles	1.026	0.926	0.817	0.690	0.828	0.750

Relative organ weights (%body weight)-Females

Organ	0 mg/kg	5 mg/kg	15 mg/kg	45 mg/kg	60 mg/kg	100 mg/kg
Liver	4.48	4.31	4.54	5.01	**5.20**	**5.22**
Uterus	1.21	1.00	0.81	0.79	0.87	0.87

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
Complete histopathology in control and high dose mice only.
Increased incidence of liver hypertrophy (hepatocelluar enlargement) at 15 mg/kg and above (groups 3-6) in males and at 60 mg/kg (group 5-6) in females. Increased lymphoid necrosis in the thymus of females at 100 mg/kg (group 6).

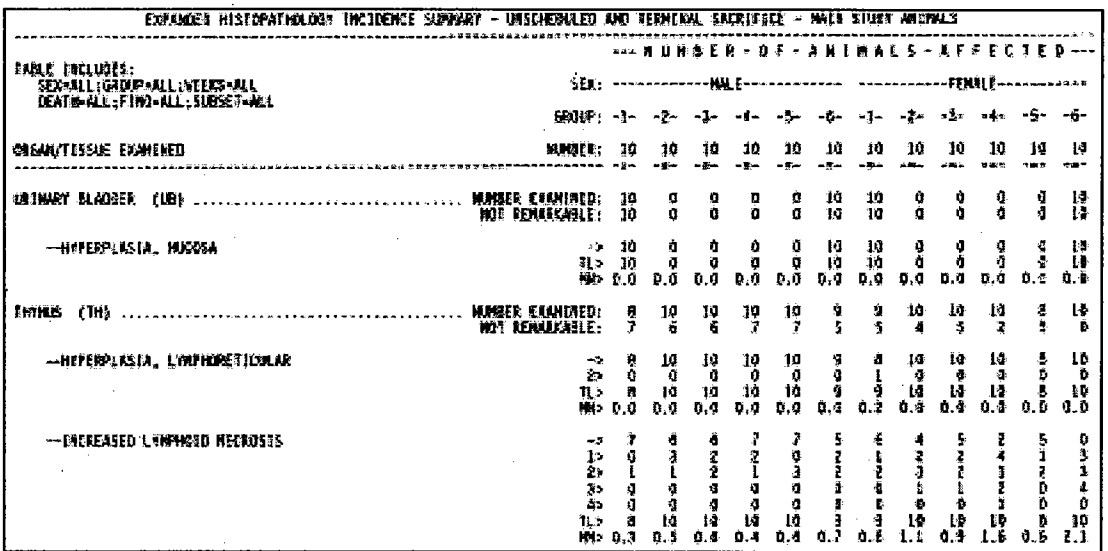


EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY - UNSCHEDULED AND TERMINAL SACRIFICE - MAIN STUDY ANIMALS

--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=ALL;FIND=ALL;SUBSET=ALL	SEX:	MALE						FEMALE					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN/TISSUE EXAMINED	NUMBER:	10	10	10	10	10	10	10	10	10	10	10	10
** TOP OF LIST **													
THYROID (TH)	NUMBER EXAMINED:	10	0	0	0	0	10	10	0	0	0	0	10
	NOT REMARKABLE:	10	0	0	0	0	10	10	0	0	0	0	10
LIVER (LI)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	3	0	0	0	10	8	10	10	8	3
--HEPATOCELLULAR ENLARGEMENT	->	10	10	3	0	0	0	10	10	10	10	9	3
	1>	0	0	6	5	2	2	0	0	0	0	1	2
	2>	0	0	1	5	7	8	0	0	0	0	0	7
	3>	0	0	0	0	1	0	0	0	0	0	0	0
	TL>	10	10	10	10	10	10	10	10	10	10	10	10
	MN>	0.0	0.0	0.0	1.5	1.9	2.2	0.0	0.0	0.0	0.0	0.1	1.6

Figure 64, from page 130 of — 2695-106



EXPANDED HISTOPATHOLOGY INCIDENCE SUMMARY - UNSCHEDULED AND TERMINAL SACRIFICE - MAIN STUDY ANIMALS

--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=ALL;FIND=ALL;SUBSET=ALL	SEX:	MALE						FEMALE					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN/TISSUE EXAMINED	NUMBER:	10	10	10	10	10	10	10	10	10	10	10	10
URINARY BLADDER (UB)	NUMBER EXAMINED:	10	0	0	0	0	10	10	0	0	0	0	10
	NOT REMARKABLE:	10	0	0	0	0	10	10	0	0	0	0	10
--HYPERPLASIA, MUCOSA	->	10	0	0	0	0	10	10	0	0	0	0	10
	TL>	10	0	0	0	0	10	10	0	0	0	0	10
	MN>	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
THYMUS (TH)	NUMBER EXAMINED:	8	10	10	10	10	9	9	10	10	10	8	10
	NOT REMARKABLE:	7	6	6	7	7	5	5	4	5	2	1	0
--HYPERPLASIA, LYMPHORETICULAR	->	8	10	10	10	10	9	8	10	10	10	8	10
	2>	0	0	0	0	0	0	1	0	0	0	0	0
	TL>	8	10	10	10	10	9	9	10	10	10	8	10
	MN>	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0
--INCREASED LYMPHOID NECROSIS	->	7	6	6	7	7	5	6	4	5	2	5	0
	1>	0	3	2	2	0	2	1	2	2	4	1	3
	2>	1	1	2	1	3	2	2	3	2	3	2	3
	3>	0	0	0	0	0	1	0	1	1	2	0	4
	4>	0	0	0	0	0	1	0	0	0	1	0	0
	TL>	8	10	10	10	10	9	9	10	10	10	8	10
	MN>	0.3	0.5	0.4	0.4	0.4	0.7	0.2	1.1	0.3	1.6	0.6	2.1

Figure 65, from page 131 of — 2695-106

Toxicokinetics:

Only 5, 45 and 60 mg/kg groups were evaluated (Groups 2, 4 and 5). Mice (2-3/sex/timepoint) were sampled at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 hours postdose on Days 1, 30 and 90.

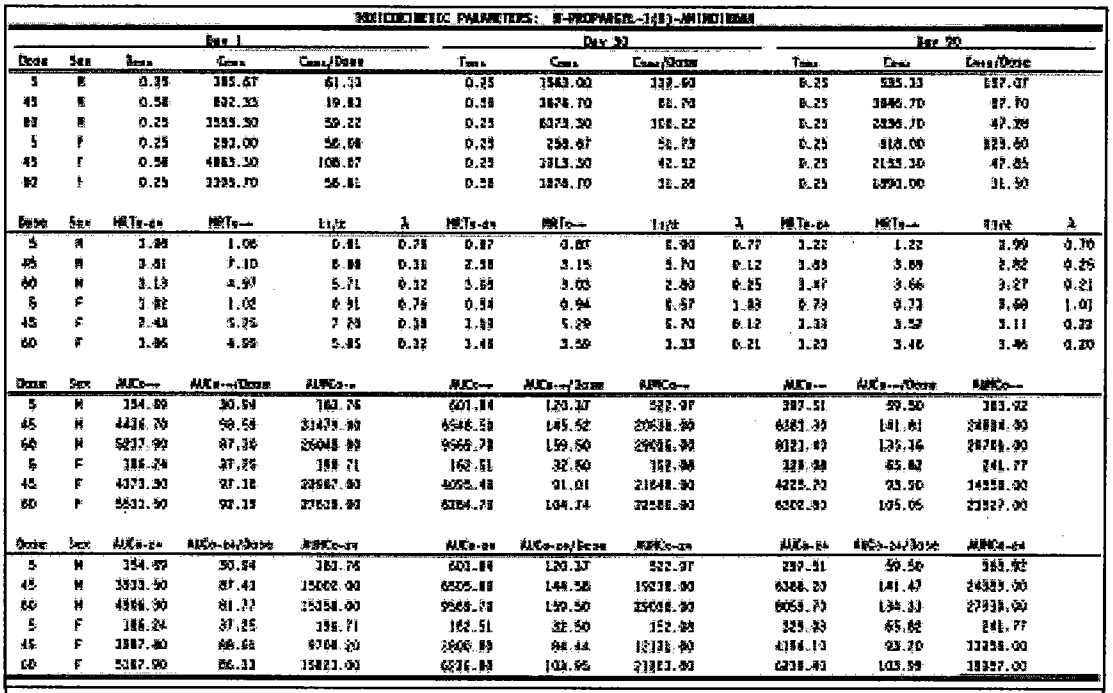


Figure 66, from page 546 of 2695-106

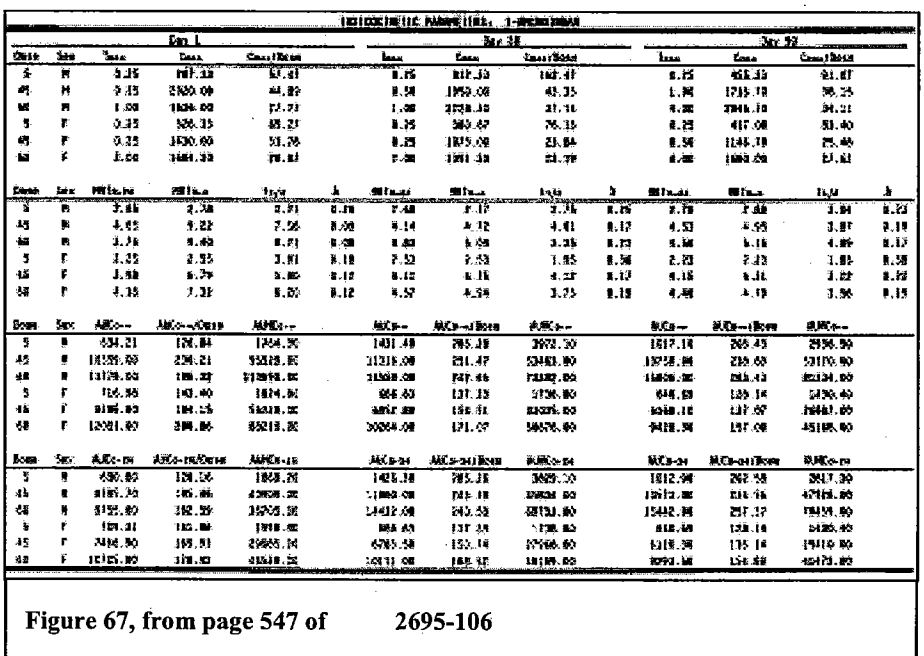


Figure 67, from page 547 of 2695-106

3.4.3.5 TVP-1012 TOXICITY TO DOGS BY REPEATED ORAL ADMINISTRATION FOR 52 WEEKS

Key study findings:
1. One dog died at 21 mg/kg (high dose).
2. Decreased body weight gain was observed at 21 mg/kg.
3. Increased cholesterol at 21 mg/kg in males and females.
4. Increased triglycerides at 21 mg/kg in males only.

Study no.: TVA 77/942506
Location: /tox/TVA 77942506.pdf
Conducting laboratory and location: [redacted]

Date of study initiation: March 11, 1993
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 255493203, [redacted] ure

Methods

Doses: 0, 0.85, 5.1 or 21 mg/kg/day
Species/strain: Dog, beagle
Number/sex/group or time point (main study): 4/sex/dose
Route, formulation, volume, and infusion rate: gelatine capsules PO
Satellite groups used for 26 week interim sacrifice: 3/sex/dose
Age: 33-40 weeks
Unique study design or methodology (if any):

Observation times and results

Mortality:
One 21 mg/kg female (564) was found dead in Week 51.

Clinical signs:
One 21 mg/kg female (564) had isolated convulsion in Week 33.

Body weights:
Dogs dosed with 21 mg/kg tended to have less body weight gain than control dogs.

Body Weight Changes in kg weeks 0-52

	0 mg/kg	0.85 mg/kg	5.1 mg/kg	21.0 mg/kg
Males	1.3	1.0	2.0	**0.0**
Females	0.8	1.2	1.3	0.4

Value in **Bold** significant at 0≤0.05

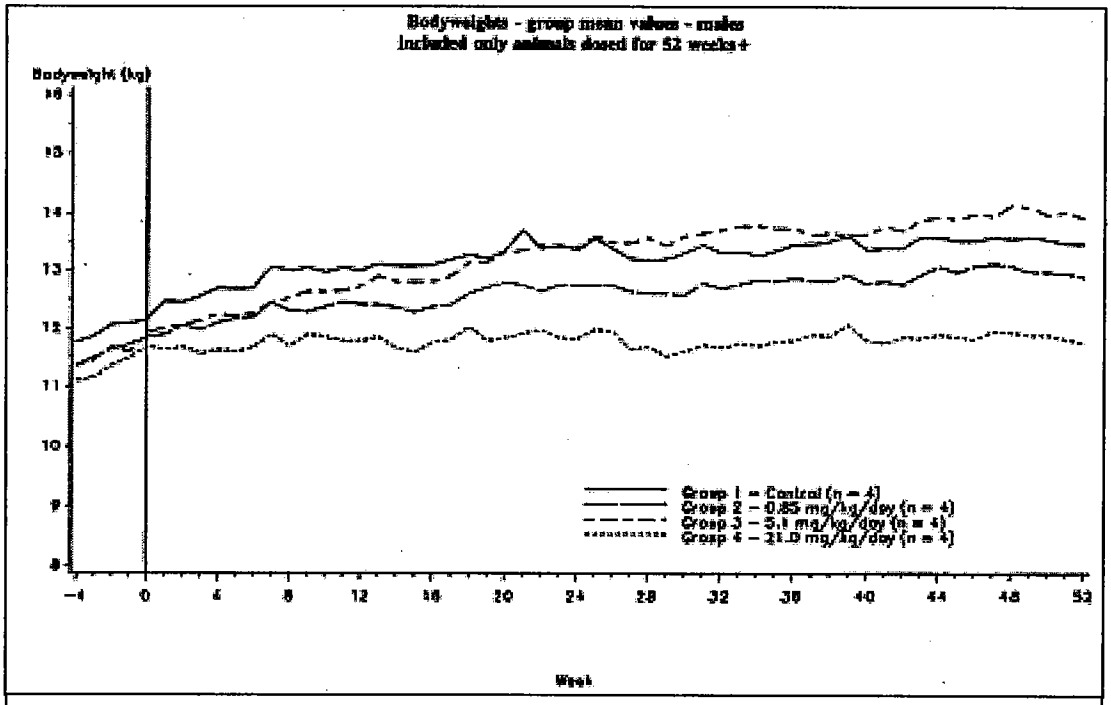


Figure 68, from page 32 of TVA 77942506

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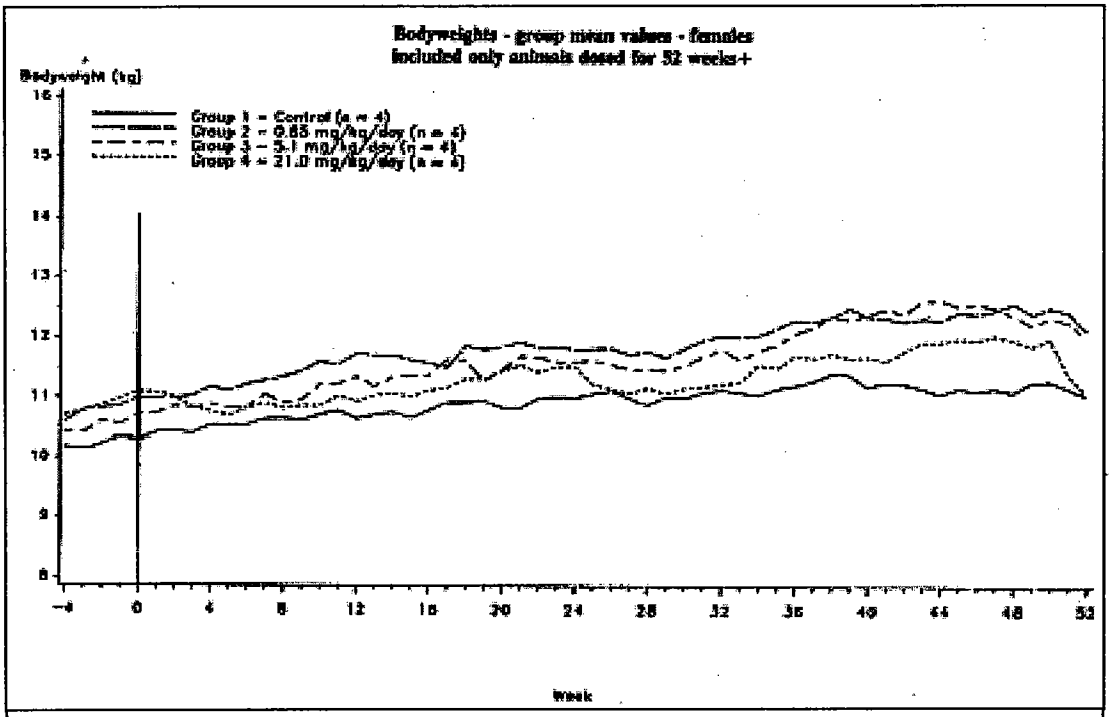


Figure 69, from page 33 of TVA 77942506

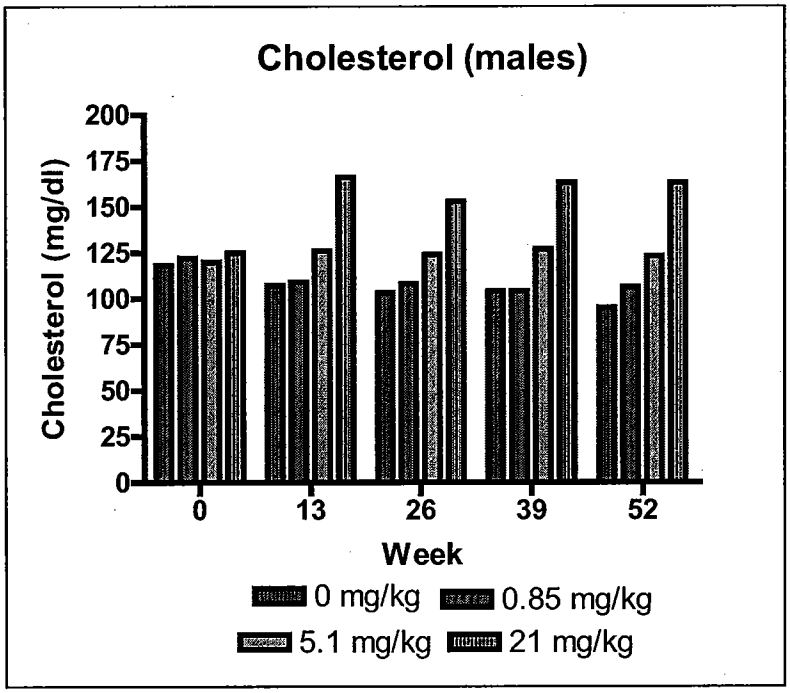
Food consumption:
No effects

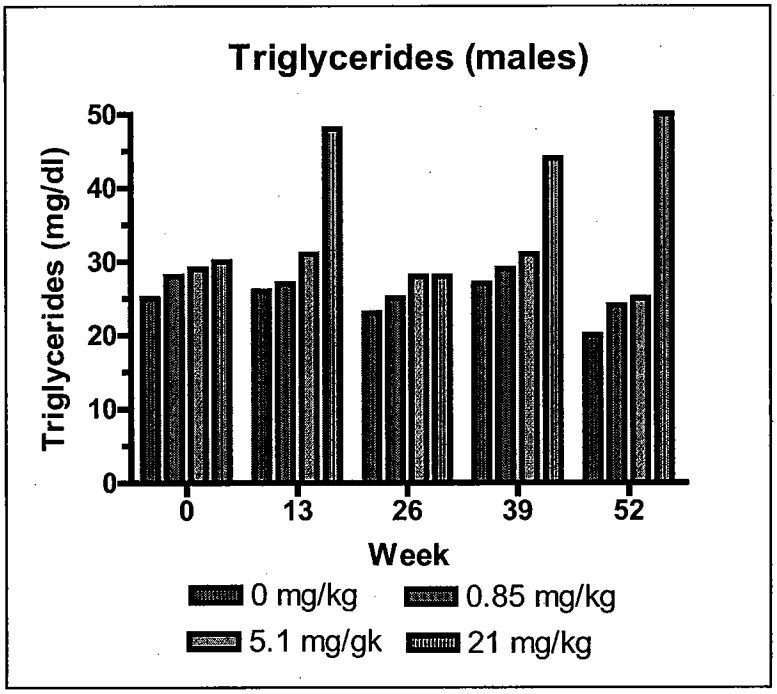
Ophthalmoscopy:
Pre, Weeks 13, 26, 39 and 52
No treatment related effects observed.

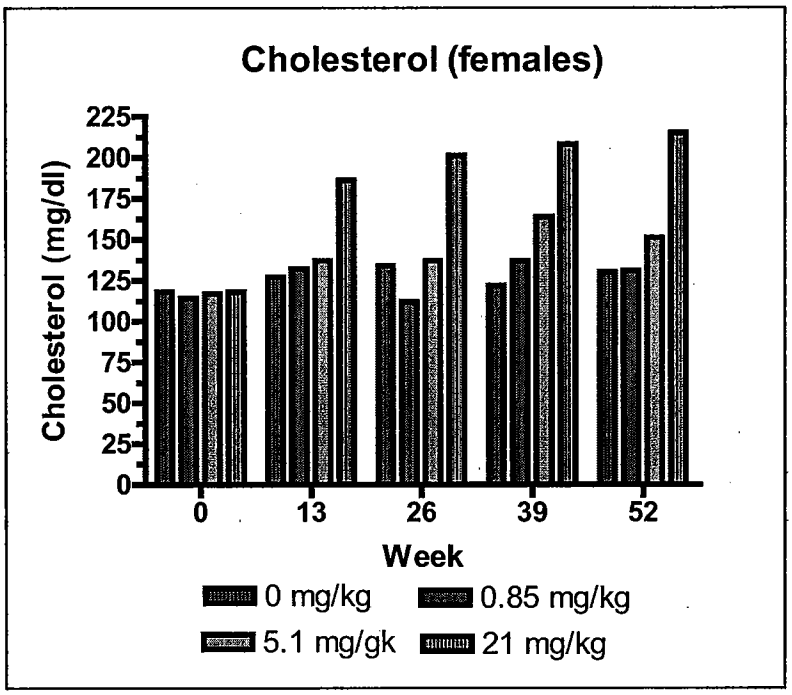
EKG:
Pre, Weeks 13, 26, 39 and 52. Only heart rates presented.
No effects on heart rate. No waveform abnormalities were observed, but no data were submitted.

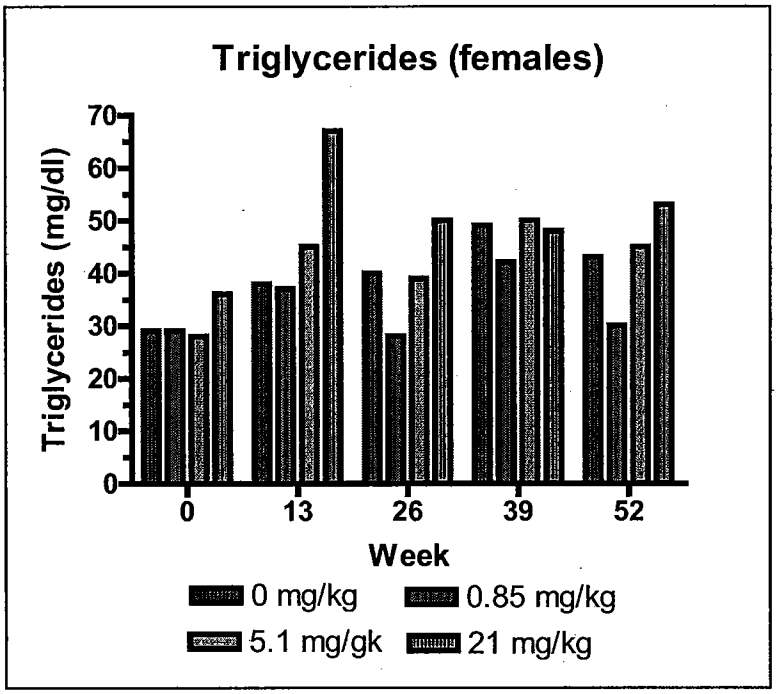
Hematology:
Pre, Weeks 13, 26, 39 and 52
No effects

Clinical chemistry:
Pre, Weeks 13, 26, 39 and 52
Increased cholesterol (males and females) and triglycerides (males only) at 21 mg/kg









Urinalysis:
No significant effects

Gross pathology:
No significant effects

Organ weights (specify organs weighed if not in histopath table):
No significant effects

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no ( )
No effects.

Toxicokinetics:
Day 0, Weeks 26 and 52; 0.75 and 6 hours post dose
Data taken from study TVA 77/950296 Addendum to TVA 77/942506

Plasma concentration of rasagiline in ng/ml

Dose Mg/kg	Sex	Day 1		Week 26		Week 52	
		0.75 hr	6 hr	0.75 hr	6 hr	0.75 hr	6 hr
0.85	M	9.0	0.1	23.6	0.9	63.1	0.4
	F	21.0	0.6	81.4	1.6	17.0	1.1
5.1	M	166.1	6.3	372.6	11.0	198.5	17.5
	F	183.6	3.8	324.3	15.1	386	10.9
21	M	3070.4	33.9	2847.8	29.6	2613.5	33.8
	F	1479.1	47	3774.7	90.2	3650.3	78.1

Plasma concentration of AI in ng/ml

Dose Mg/kg	Sex	Day 1		Week 26		Week 52	
		0.75 hr	6 hr	0.75 hr	6 hr	0.75 hr	6 hr
0.85	M	29.0	3.4	21.1	6.0	23.0	6.3
	F	24.3	3.4	28.2	5.6	18.2	5.0
5.1	M	174.9	31.5	281.8	64.2	161.1	74.1
	F	308.1	36.6	242.3	70.3	303.8	69.0
21	M	1222.3	285.1	1175.0	446.8	1042.5	263.1
	F	933.0	308.7	1015.0	519.2	925.0	432.2

Other:

3.4.3.6 TOXICITY STUDY OF RASAGILINE MESYLATE (TVP-1012) BY ORAL CAPSULE ADMINISTRATION IN COMBINATION WITH 80/20 MG/KG/DAY LEVODOPA/CARBIDOPA IN THE BEAGLE DOGS FOR 13 WEEKS FOLLOWED BY AN 8 WEEK RECOVERY PERIOD

Key study findings:

1. The combination of 2 mg/kg rasagiline with levodopa/carbidopa caused circling behavior (suggestive of stereotypic behavior). Circling behavior was also observed in one dog receiving 1 mg/kg rasagiline with levodopa/carbidopa.
2. Reduced body weight gain was observed at 2 mg/kg rasagilne with levodopa/carbidopa.
3. Levodopa/carbidopa caused emesis in treated dogs at all doses.
4. Rasagiline alone had no adverse effects in this study.
5. No significant effects were noted on toxicokinetic parameters.

Study no.: TVA 165/023224
Location: /tox/TVA 165023224
Conducting laboratory and location: —
Date of study initiation: July 25, 2001
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: J14K0250, — , pure

Methods

Doses: See table below
Species/strain: Dog, beagle
Number/sex/group or time point (main study): 4/sex/dose
Route, formulation, volume, and infusion rate: Oral capsules
Satellite groups used for recovery: 2/sex, groups 1 and 6 only
Age: 18-24 weeks
Weight (nonrodents only): 6.8-10.0 kg (males), 5.7-9.3 kg (females)
Unique study design: Rasagiline was administered with the first LD/CD dose

Group	1st daily dose Treatment	Dosage mg/kg	2nd daily dose Treatment	Dosage mg/kg
1	Empty capsules	-	Empty capsules	-
2	LD/CD	40/10	LD/CD	40/10
3	Rasagiline	2.0	Empty capsules	-
4	Rasagiline	0.3	-	-
	LD/CD	40/10	LD/CD	40/10
5	Rasagiline	1.0	-	-
	LD/CD	40/10	LD/CD	40/10
6	Rasagiline	2.0	-	-
	LD/CD	40/10	LD/CD	40/10

Figure 70, from page 22 of Report TVA 165023224

each day; second LD/CD dose was 8 hours after the first LD/CD dose.

Observation times and results

Mortality:
Group 6 male #725 was sacrificed humanely during week 12 due to abnormal behavior (circling behavior). This dog had lost 0.8 kg between week 10 and 11.

Clinical signs: 1X/day
One female in Group 5 and 3 males and 1 female in Group 6 had circling behavior (stereotypy) from week 10 onwards.
All dogs treated with levodopa/carbidopa vomited 30-90 minutes after the first dose each day.

Body weights:
Decreased weight gain was observed in dogs treated with levodopa/carbidopa.

Body weight gain in kg weeks 0-13

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Males	4.4	**3.1**	4.3	3.3	3.2	4.1
Females	3.9	3.0	3.5	2.8	2.8	2.7

Values in **Bold** significantly different from controls ($p<0.05$).

APPEARS THIS WAY
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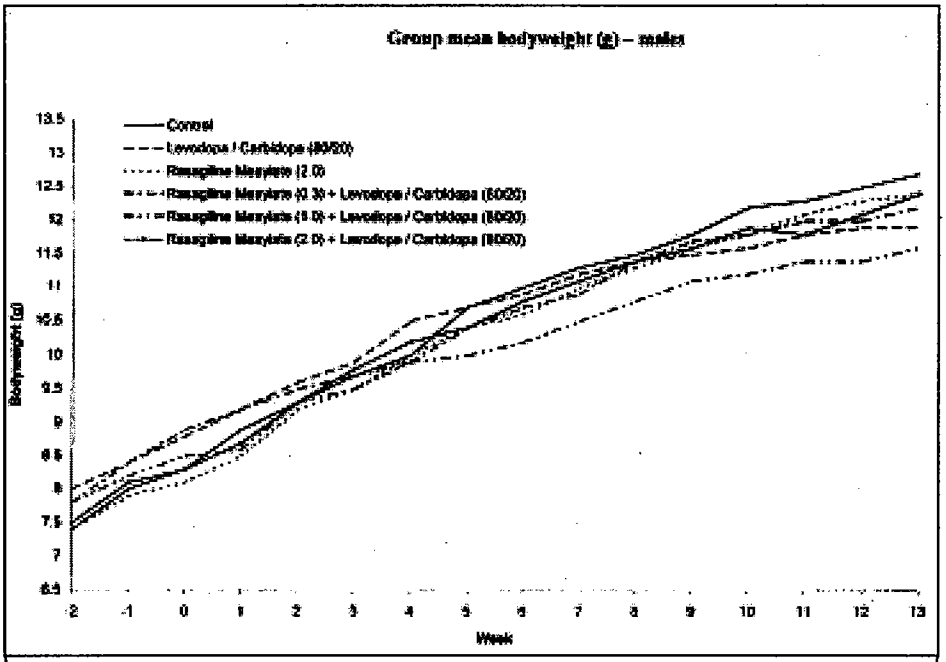


Figure 71, from page 49 of Report TVA 165/023224

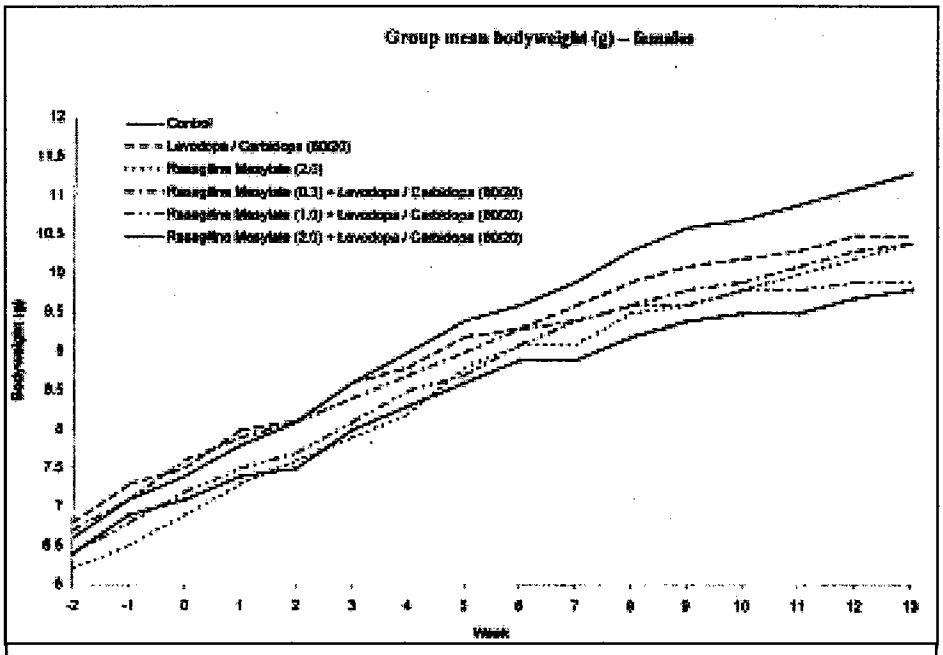
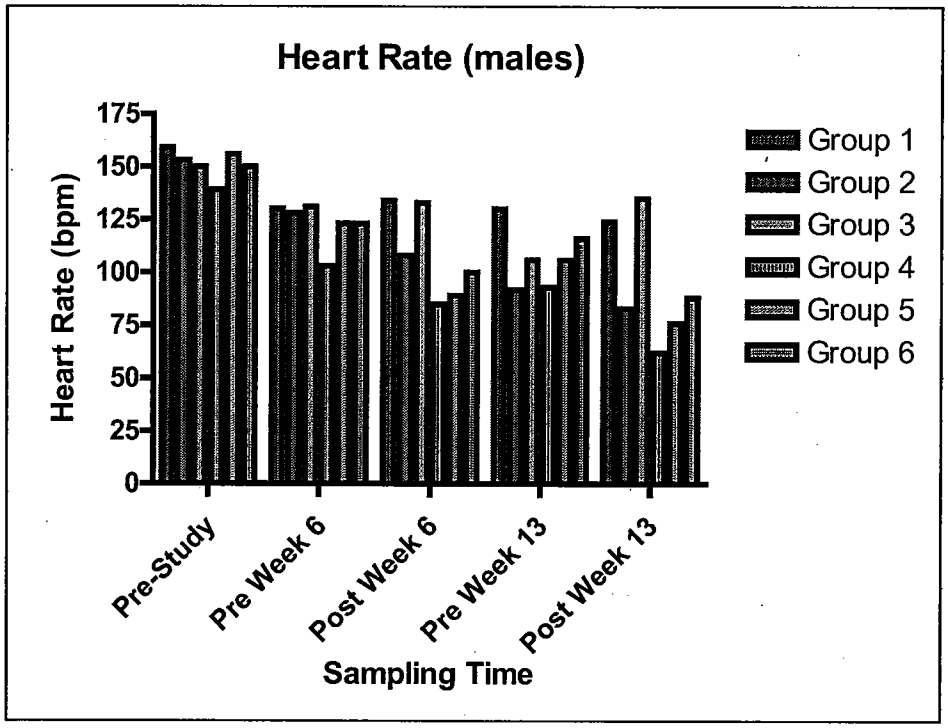


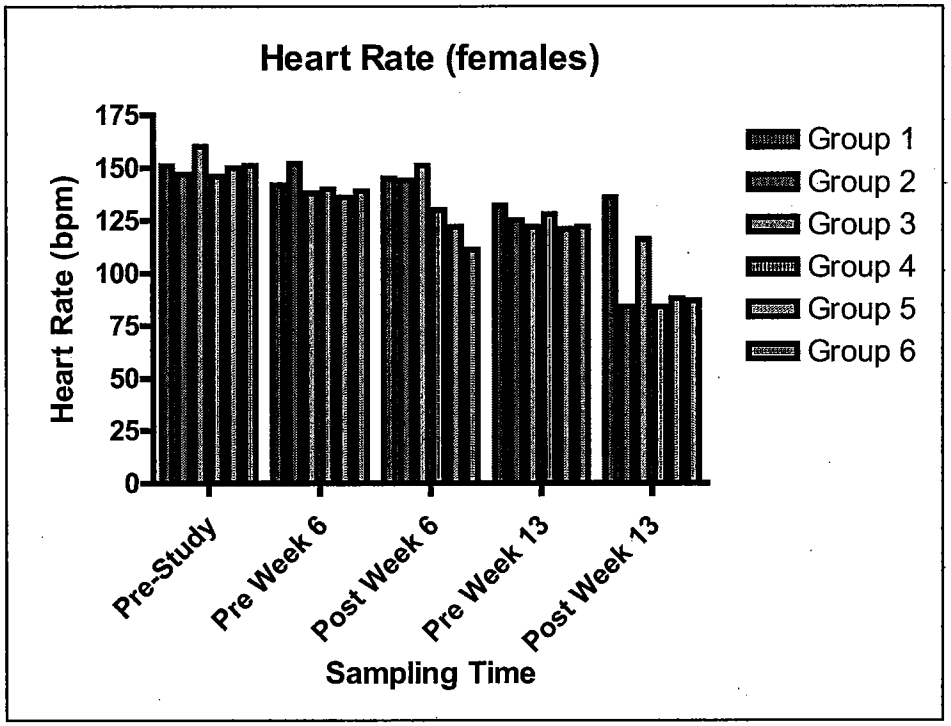
Figure 72, from page 50 of Report TVA 165/023224

Food consumption: 1X/week
Decreased food consumption was observed in all dogs treated with levodopa.

Ophthalmoscopy: Pre, week 13
No effects observed

EKG: Prestudy (3X), Week 6, 13; predose and 2 hours post AM dose; QT interval was corrected using QTcv adjustment
Decreased heart rate was associated with levodopa treatment, but no effects on corrected QT intervals. In the graph below, the three prestudy values are presented as an average. Pre week 6 and pre week 13 refer to values taken prior to drug administration; post week 6 and post week 13 refer to values taken two hours after the morning dosing.





Hematology: Pre, Weeks 6, 13
No significant effects were observed.

Clinical chemistry:
No significant effects were observed.

Urinalysis:
No significant effects were observed.

Gross pathology:
No significant effects were observed.

Organ weights (specify organs weighed if not in histopath table):
No significant effects were noted on organ weights.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)
One group 6 female dog had minimal to slight basophilic cortical tubules in the kidney.
Thymic involution was noted in all male dogs receiving levodopa and in group 6 females; this lesion was not observed after the recovery period.
No other significant effects were observed.

Toxicokinetics: Week 6, 0, 0.5, 1, 2, 4 and 8 hours post dose; no significant effects.

PAI exposure

Dose level (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
2.0[a]	100.88	72.28	164.2	120.8
	(79.95)	(46.14)	(109.1)	(72.5)
0.3	11.89	22.62	21.0	34.6
	(15.17)	(24.29)	(14.8)	(26.9)
1.0	22.20	25.05	37.8	55.8
	(12.93)	(11.72)	(19.4)	(25.5)
2.0	79.30	113.44	90.9	150.4
	(73.41)	(72.46)	(56.3)	(98.7)

[a] Levodopa/Carbidopa were not administered to this group

Figure 73, from page 38 of Report TVA 165023224

AI

Dose level (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
2.0[a]	50.59	81.31	153.7	232.0
	(18.38)	(20.41)	(53.3)	(63.8)
0.3	3.88	7.95	15.5	22.6
	(1.11)	(4.79)	(9.4)	(10.8)
1.0	25.11	30.29	76.8	97.2
	(28.41)	(10.14)	(55.2)	(33.9)
2.0	45.82	63.50	138.5	178.2
	(19.76)	(27.42)	(71.6)	(59.5)

[a] Levodopa/Carbidopa were not administered to this group

LD

Dose level of Rasagiline (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
0	12182.9	8119.3	24630	23520
	(7623.7)	(2558.9)	(19644)	(9895)
0.3	4123.9	8541.1	13484[a]	17884
	(3328.3)	(6834.8)	(-)	(10504)
1.0	9487.9	7813.5	27146	23670
	(7757.5)	(1753.1)	(16133)	(9499)
2.0	12259.7	7040.2	17827	17680
	(6733.4)	(3308.4)	(8637)	(12605)

[a] Value available from one animal

CD

Dose level of Rasagiline (mg/kg/day)	C_{max} (ng/ml) Males	C_{max} (ng/ml) Females	AUC_t (ng.h/ml) Males	AUC_t (ng.h/ml) Females
0	1354.3	677.1	4267	2033
	(1119.6)	(466.5)	(3635)	(1486)
0.3	1091.4	1598.2	2951	4727
	(694.4)	(1294.3)	(-)	(3994)
1.0	738.9	1833.3	2637	5795
	(825.8)	(1195.8)	(3031)	(3992)
2.0	750.9	1491.1	2284	4654
	(254.9)	(1071.0)	(1162)	(3145)

Figure 74, from page 39 of Report TVA 165023224

3.4.4. Genetic toxicology

3.4.4.1 TVP-1012 (BATCH P92208) BACTERIAL MUTATION ASSAY

Key findings: Rasagiline did not induce mutations in the Ames assay.

Study no.: TVA 64B/920799

Location: /tpx/TVA 64B920799.pdf
Conducting laboratory and location:

Date of study initiation: May 18, 1992
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch P92208

Methods
Both plate incorporation (experiment 1) and pre-incubation (experiment 2) methods were used.

Strains/species/cell line:
Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537

Doses used in definitive study:
50, 150, 500, 1500, 5000 ug/plate

Basis of dose selection: Limit dose (5000 ug/plate)

Negative controls: Vehicle (water)

Positive controls:

Strain	-S9	+S9
TA98	2-Nitrofluorene (80 ug/plate)	2-Aminoanthracine (0.5 ug/plate)
TA100	N-Ethyl-N'-nitro-N-nitrosoguanidine (3 ug/plate)	2-Aminoanthracine (1 ug/plate)
TA102	Mitomycin C (0.5 ug/plate)	1,8-Dihyroxyanthraquinone (30 ug/plate)
TA1535	N-Ethyl-N'-nitro-N-nitrosoguanidine (5 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA1537	9-Aminoacridine (80 ug/plate)	2-Aminoanthracine (2 ug/plate)

Metabolic Activation System:
Aroclor 1254 pretreated male rat hepatic S9

Incubation and sampling times:
Plates counted after 72 hours

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): Adequate doses were used. The positive controls were positive and the negative controls were negative. In experiment 2, excessive toxicity was observed at 5000 ug/plate in the presence of S9 in TA102 and TA1535, but this does not affect the validity of the study.

Study outcome: The results are presented below. Rasagiline did not show mutagenic potential in this test system.

Mean revertants/plate in experiment 1 (plate incorporation assay)

	TA98		TA100		TA102		TA1535		TA1537	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	21	24	99	107	149	188	12	14	14	16
0	22	22	108	102	163	192	11	12	12	15
50	25	24	105	113	176	162	12	14	14	16
150	23	21	106	111	164	175	9	13	13	17
500	24	24	96	104	135	172	13	13	13	15
1500	22	24	114	116	164	172	15	14	14	14
5000	24	25	108	130	152	173	10	12	12	12
PC	189	275	327	633	518	810	246	236	TMC	108

PC = Positive control
TMC = "Too many colonies to count accurately"

Mean revertants/plate in experiment 2 (pre-incubation assay)

	TA98		TA100		TA102		TA1535		TA1537	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	26	31	98	116	205	216	14	15	16	15
0	27	25	112	115	189	216	11	14	16	16
50	27	25	84	97	224	224	11	14	13	12
150	22	26	88	104	182	232	13	12	18	18
500	19	27	103	125	189	222	11	10	14	18
1500	26	30	92	125	207	206	12	10	13	14
5000	14	20	90	IL	114	IL	12	12	15	12
PC	275	215	329	461	700	974	188	57	TMC	124

PC = Positive control
IL = Incomplete bacterial lawn
TMC = "Too many colonies to count accurately"

3.4.4.2 TVP-1012 (BATCH 23029101-132) BACTERIAL MUTATION ASSAY

Key findings: Rasagiline did not induce mutations in the Ames assay.

Study no.: TVA 64C/920800

Location: /tox/TVA 64C920800.pdf
Conducting laboratory and location:

Date of study initiation: May 18, 1992
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch 23029101-132

Methods
Both plate incorporation (experiment 1) and pre-incubation (experiment 2) methods were used.

Strains/species/cell line:
Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537

Doses used in definitive study:
50, 150, 500, 1500, 5000 ug/plate

Basis of dose selection: Limit dose (5000 ug/plate)

Negative controls: Vehicle (water)

Positive controls:

Strain	-S9	+S9
TA98	2-Nitrofluorene (80 ug/plate)	2-Aminoanthracine (0.5 ug/plate)
TA100	N-Ethyl-N'-nitro-N-nitrosoguanidine (3 ug/plate)	2-Aminoanthracine (1 ug/plate)
TA102	Mitomycin C (0.5 ug/plate)	1,8-Dihyroxyanthraquinone (30 ug/plate)
TA1535	N-Ethyl-N'-nitro-N-nitrosoguanidine (5 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA1537	9-Aminoacridine (80 ug/plate)	2-Aminoanthracine (2 ug/plate)

Metabolic Activation System:
Aroclor 1254 pretreated male rat hepatic S9

Incubation and sampling times:
Plates counted after 72 hours

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): Adequate doses were used. The positive controls were positive and the negative controls were negative. In experiment 2, excessive toxicity was observed at 5000 ug/plate in the presence of S9 in TA102 and TA1535, but this does not affect the validity of the study.

Study outcome: The results are presented below. Rasagiline did not show mutagenic potential in this test system.

Mean revertants/plate in experiment 1 (plate incorporation assay)

	TA98		TA100		TA102		TA1535		TA1537	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	21	24	99	107	149	188	12	14	12	16
0	22	22	108	102	163	192	11	12	11	16
50	20	23	112	99	158	163	10	14	10	13
150	22	23	100	104	182	174	13	16	12	13
500	20	24	99	109	154	159	12	14	15	13
1500	23	21	100	106	161	168	13	13	14	16
5000	21	27	104	127	155	160	12	16	13	14
PC	189	275	327	633	518	810	246	236	TMC	108

PC = Positive control
TMC = "Too many colonies to count accurately"

Mean revertants/plate in experiment 2 (pre-incubation assay)

	TA98		TA100		TA102		TA1535		TA1537	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	26	31	98	116	205	216	14	15	16	15
0	27	25	112	115	189	216	11	14	16	16
50	23	27	118	103	224	212	8	11	17	16
150	21	24	92	117	211	235	15	12	15	15
500	26	31	93	116	195	224	10	12	15	18
1500	24	20	99	136	218	220	15	11	17	17
5000	23	24	94	90	111	124	10	7	12	16
PC	275	215	329	461	700	974	188	57	TMC	124

PC = Positive control
IL = Incomplete bacterial lawn
TMC = "Too many colonies to count accurately"

3.4.4.3 TV-5701182 ASSESSMENT OF MUTAGENIC POTENTIAL IN HISTIDINE AUXOTROPHS OF SALMONELLA TYPHIMURIUM (THE AMES TEST)

Key findings: Rasagiline did not induce mutations in the Ames assay. This study is considered incomplete since it did not include an assessment of AT point mutations (study did not include S. typhimurium TA 102 or E. coli WP2) and there were methodological problems (eg duplicate rather than triplicate cultures) and lab errors (contaminated cultures).

Study no.: TEV/054/TV

Location: /tox/TEV054TV.pdf
Conducting laboratory and location: —

Date of study initiation: February 1990
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Batch 23028901-121

Methods
Plate incorporation method was used.

Strains/species/cell line:
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538

Doses used in definitive study: 25, 125, 625, 1250, 2500 ug/plate

Basis of dose selection: Reduced lawn at 5000 ug/plate

Negative controls: Vehicle (water)

Positive controls:

Strain	-S9	+S9
TA98	4-Nitro-o-phenylenediamine (20 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA100	Sodium Azide (3 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA1535	Sodium Azide (3 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA1537	ICR-191 (2 ug/plate)	2-Aminoanthracine (2 ug/plate)
TA1538	4-Nitro-o-phenylenediamine (20 ug/plate)	2-Aminoanthracine (2 ug/plate)

Metabolic Activation System:
Phenobarbital/3-methylcholanthrene pretreated male rat hepatic S9

Incubation and sampling times:
Duplicate plates counted after 48 hours

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): Adequate doses were used. The positive controls were positive and the negative controls were negative. Only duplicate plates (rather than triplicates) were used. Cultures were incubated for 48 hours rather than 72 hours. 2-Aminoanthracene did not induce mutations in the absence of S9 (data not presented). Six plate were contaminated. The solvent control in the TA1538 with metabolic activation (experiment 1) was unexpectedly low.

Study outcome: The results are presented below. Rasagiline did not show mutagenic potential in this test system.

Mean revertants/plate in experiment 1

	TA98		TA100		TA1535		TA1537		TA1538	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	16	18	44	58	15	10	12	6	12	4
0	12	--	42	--	26	--	20	--	20	--
25	14	26	42	36	15	8	18	8	18	44
125	16	16	20	69	21	18*	25	6*	18	30
625	12	41*	30	58	26	14	20	14	18	25
1250	12	35	32	58	32	16	18	16	12	29*
2500	14	24	29	56	29	16	18	16	30	28
PC	1510	370	277	170	2290	135	1480	234	1732	1272

PC = Positive control
* = single plate; duplicate plate had contamination.

Mean revertants/plate in experiment 2

	TA98		TA100		TA1535		TA1537		TA1538	
Dose	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Water	24	30	78	54	24	14	6	10	15	24
0	6	--	73	--	20	--	10	--	12	--
25	14	C	96	41	8	14	7	10	10	12
125	10	9*	86	62	14	17	6	8	14	17*
625	10	17	32	32	28	18	4	4	10	22
1250	16	24	62	62	22	16	5	8	18	12
2500	8	19	38	38	26	20	4	7	18	12
PC	1378	409	308	98	2104	119	2390	370	2692	3136

PC = Positive control
* = single plate; duplicate plate had contamination.
C = both plates were contaminated

3.4.4.4 STUDY TO EVALUATE THE CHROMOSOME DAMAGING POTENTIAL OF TVP-1012 BY ITS EFFECTS ON CULTURED HUMAN PERIPHERAL BLOOD LYMPHOCYTES USING AN IN VITRO CYTOGENETICS ASSAY

Key findings:
Rasagiline induced a significant increase in the incidence of chromosomal aberrations in the presence of metabolic activation, but not in the absence of metabolic activation.

Study no.: 1 ETIP.015 TIP 15

Location: /tox/1 ETIP.015 TIP 15 102816.pdf
Conducting laboratory and location: —

Date of study initiation: November 4,1992
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: P-92214, >

Methods

Strains/species/cell line:
Human Peripheral Lymphocytes

Doses used in definitive study:

Basis of dose selection:
50-80% decrease in Mitotic Index in Dose Range Finding Study.

Negative controls:
Vehicle (water)

Positive controls:
4-Nitroquinoline 1-oxide (1.25, 2.5, 5.0 ug/ml) -S9
Cyclophosphamide (1.25, 2.5 ug/ml) +S9

Metabolic Activation System:
Aroclor 1254 pretreated male rat hepatic S9 (dosage and duration not given). Media contrained 5% of S9 mixture.

Incubation and sampling times:
-S9- 20 hour incubation (trial 1)
-S9- 44 hour incubation (trial 1) [not evaluated]
-S9- 3 hour incubation with 41 hour recovery (trial 2) [not evaluated]
+S9- 3 hour incubation with 17 hour recovery (trials 1 and 2) [only one trial done)

Results

Study validity (comment on replicates, criteria for positive results, etc.):
The methods were appropriate. The positive and negative controls gave appropriate responses. The study is considered valid.

Study outcome:
Rasagiline caused an increase in the incidence of chromosomal aberrations at 63.5 ug/ml and above in the presence of metabolic activation. No increase was observed in the absence of metabolic activation. Due to the positive result in the first study, the other planed studies were not conducted.

Incidence of Aberrations in the Absence of Metabolic Activation after 20 hours of Treatment

Dose ug/ml	Cell	Gap	Chr del	Chr exch	Ctd del	Ctd exch	Other	Abs +gap	Abs -gap (%Abs)	Num Abs	MI
0	200	1	2	0	2	0	0	5	4 (2.0)	2	5.5
89	200	2	1	0	1	0	0	4	2 (1.0)	3	4.8
211	200	1	0	1	2	0	0	3	2 (1.0)	3	3.5
667	200	5	1	0	2	0	0	7	3 (1.5)	1	3.0
890	200	3	2	0	3	0	0	8	5 (2.5)	1	1.9
1190	200	1	1	0	5	0	0	7	6 (3.0)	0	2.2
NQO	50	5	4	0	15	7	5	23	22 (44)	0	

Abs refers to number of cells with aberrations (cells may have more than one type of aberration).

Incidence of Aberrations in the Presence of Metabolic Activation after 3 hours of Treatment followed by17 hours of Recovery

Dose ug/ml	Cell	Gap	Chr del	Chr exch	Ctd del	Ctd exch	Other	Abs +gap	Abs -gap (%Abs)	Num Abs	MI
0	200	2	1	0	2	0	0	5	3 (1.5)	1	5.2
6.36	200	2	0	0	1	0	0	3	1 (0.5)	4	5.4
20.1	200	3	0	0	0	0	0	3	0 (0.0)	5	5.1
35.7	200	6	1	0	5	0	0	10	5 (2.5)	4	3.4
63.5	200	5	6	0	19	0	0	17	**15 (7.5)**	14	3.3
113	200	17	2	0	17	3	2	30	***20 (10.0)***	16	2.4
2670	200	18	2	0	25	2	2	37	***26 (13.0)***	6	3.8
CPA	50	11	5	0	14	0	0	19	***15 (30.0)***	0	---

Abs refers to number of cells with aberrations (cells may have more than one type of aberration).
Values in **Bold** were statistically significant ($p \leq 0.01$)
Values in ***Bold Italic*** were statistically significant ($p \leq 0.001$)

Abbreviations and classification of observations

abs	=	aberrations
tot	=	total
rep	=	replicate

Gaps (g)

csg	=	chromosome gap
ctg	=	chromatid gap

Chromosome deletions (Chr del)

del	=	chromosome deletion
d min	=	double minute
f	=	isolocus fragment

Chromosome exchanges (Chr exch)

t	=	interchange between chromosomes (eg reciprocal translocation)
inv	=	chromosome intrachange (eg pericentric inversion)
dic	=	dicentric
dic+f	=	dicentric with accompanying fragment
acr	=	acentric ring
r+f	=	centric ring with accompanying fragment
r	=	centric ring

Chromatid deletions (Ctd del)

del	=	chromatid deletion
su	=	isochromatid deletion with sister union of broken ends
nud	=	isochromatid deletion with non-union of broken ends distally
nup	=	isochromatid deletion with non-union of broken ends proximally
sin	=	single minute

Chromatid exchanges (Ctd exch)

qr	=	interchange between chromatids of different chromosomes (eg quadriradial)
cx	=	obligate complex interchange
e	=	chromatid intrachange
tr/tr+f	=	isochromatid/chromatid interchange (eg triradial)

Other structural aberrations

pvz	=	pulverised
mabs	=	multiple aberrations (greater than 7 aberrations per cell or too many aberrations to permit accurate analysis)

Numerical aberrations (num abs)

E	=	endoreduplicated
H	=	hyperdiploid (47-68 chromosomes)
P	=	polyploid (greater than 68 chromosomes)

Figure 75, from page 30 of Report 1 £TIP.015 TIP 15'

3.4.4.5 RASAGILINE MESYLATE (TVP-1012) IN A CHROMOSOMAL ABERRATIONS ASSAY IN CULTURED HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN THE PRESENCE AND ABSENCE OF 1 MM GLUTATHIONE UNDER METABOLIC ACTIVATION CONDITIONS

Key findings:
Rasagiline induced a significant increase in the incidence of chromosomal aberrations in the presence of metabolic activation 20 hours, but not after 41 hours. No increase was observed in the presence of glutathione, but no positive control was tested in the presence of metabolic activation. In addition, the high dose of rasagiline did not induce significant cytotoxicity in the 46 hour sampling time, suggesting that higher doses should have been used at this time point.

Study no.: 18585-0-449OECD

Location: \pharmtox\tox\18585-0-449OECD.pdf
Conducting laboratory and location:
Date of study initiation: August 6,1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: CN:255495223, — pure

Methods
Cells were incubated with and without 1 mM glutathione.

Strains/species/cell line:
Human Peripheral Lymphocytes

Doses used in definitive study:
See below

Basis of dose selection:
50-80% decrease in Mitotic Index in Dose Range Finding Study.

Negative controls:
Vehicle (water)

Positive controls:
Cyclophosphamide (50, 100 or 150 ug/ml) +S9

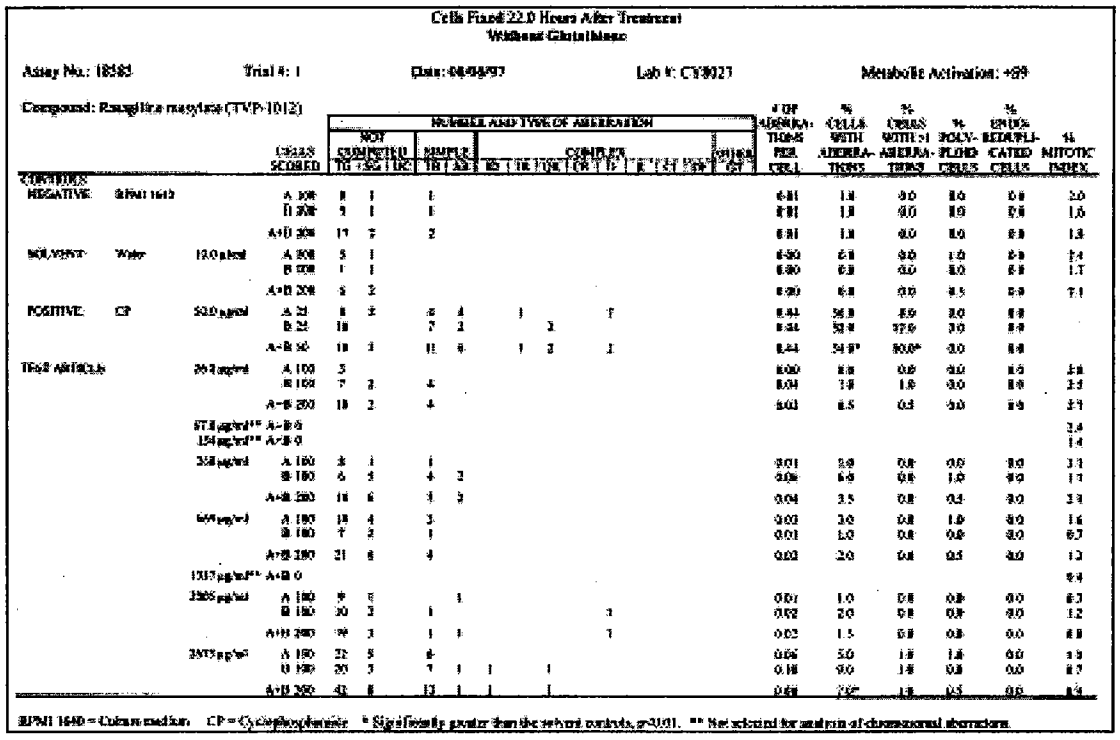
Metabolic Activation System:
Hepatic S9 from male rats pretreated with 500 mg/kg/day Aroclor 1254 for 5 days. Concentration in the test media was not given.

Incubation and sampling times:
+S9- 3 hour incubation with 17 hour or 41 hour recovery

Results

Study validity (comment on replicates, criteria for positive results, etc.):
The methods were appropriate. The positive and negative controls gave appropriate responses. The positive control (cyclophosphamide) was not tested in the presence of glutathione which makes it difficult to interpret the glutathione data. The high dose in the presence of glutathione 46 hours after treatment did not induce significant cytotoxicity (MI was 70% of control) suggesting that higher doses should have been used.

Study outcome:
Rasagiline caused an increase in the incidence of chromosomal aberrations at the highest dose only (2673 ug/ml) after 3 hour treatment and a 17 hour recovery (cells fixed 22 hours after treatment). No increase in aberrations were observed after a three hour treatment followed by a 41 hour recovery period. No increases were observed in the presence of glutathione, but the lack of a positive control with glutathione treatment makes it impossible to interpret the data (does glutathione interfere with the expression of aberrations in a specific or non-specific matter).



Cells Fixed 22.0 Hours After Treatment
Without Glutathione

Assay No.: 18585 Trial #: 1 Date: 04/04/97 Lab #: CYB027 Metabolic Activation: +S9

Compound: Rasagiline mesylate (TVP-1012)

CONDITIONS			CELLS SCORED	NUMBER AND TYPE OF ABERRATION	# OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS	% POLYPLOID CELLS	% ENDOREDUPLICATED CELLS	% MITOTIC INDEX
NEGATIVE:	RPMI 1640		A 100	0 1	0.01	1.0	0.0	0.0	0.0	2.0
			B 100	0 1	0.01	1.0	0.0	0.0	0.0	1.6
			A+B 200	0 2	0.01	1.0	0.0	0.0	0.0	1.8
SOLVENT:	Water	12.0 µl/ml	A 100	0 1	0.01	1.0	0.0	1.0	0.0	2.4
			B 100	0 1	0.01	1.0	0.0	0.0	0.0	1.7
			A+B 200	0 2	0.01	2.0	0.0	0.5	0.0	2.1
POSITIVE:	CP	50.0 µg/ml	A 25	0 2	4 4	1	1	56.0	8.0	0.0
			B 25	10	7 3		3	52.0	12.0	8.0
			A+B 50	10 2	11 6	1 3	1	54.0*	10.0	8.0
TEST ARTICLE:		267 µg/ml	A 100	0				0.00	0.0	0.0	2.0
			B 100	0 2	4			0.04	2.0	1.0	0.0	0.0	2.5
			A+B 200	0 2	4			0.02	2.0	0.5	0.0	0.0	2.3
		87.8 µg/ml**	A+B 0										2.4
		154 µg/ml**	A+B 0										1.4
		358 µg/ml	A 100	0 1	1			0.01	1.0	0.0	0.0	0.0	2.1
			B 100	0 5	4 2			0.06	6.0	0.0	1.0	0.0	1.7
			A+B 200	0 6	5 3			0.04	3.5	0.0	0.5	0.0	2.3
		669 µg/ml	A 100	0 4	3			0.03	3.0	0.0	1.0	0.0	1.6
			B 100	0 2	1			0.01	1.0	0.0	0.0	0.0	0.7
			A+B 200	0 6	4			0.02	2.0	0.0	0.5	0.0	1.2
		1317 µg/ml**	A+B 0										0.4
		2505 µg/ml	A 100	0 5	1			0.01	1.0	0.0	0.0	0.0	0.3
			B 100	0 3	1		1	0.02	2.0	0.0	0.0	0.0	1.2
			A+B 200	0 8	1 1		1	0.02	1.5	0.0	0.0	0.0	0.8
		2673 µg/ml	A 100	0 5	4			0.04	3.0	1.0	1.0	0.0	1.3
			B 100	0 3	1 1	1		0.08	8.0	1.0	0.0	0.0	0.7
			A+B 200	0 8	5 1	1		0.06	5.0*	1.0	0.5	0.0	0.9

RPMI 1640 = Culture medium CP = Cyclophosphamide * Significantly greater than the solvent controls, p<0.01. ** Not selected for analysis of chromosomal aberrations.

Figure 76, from page 18 of Report 18585-0-449OECD

Cells Fixed 22.0 Hours After Treatment
With Glutathione

Assay No.: 18585   Trial #: 1   Date: 08/06/97   Lab #: CY9023   Metabolic Activation: +S9

Compound: Rasagiline mesylate (TVP-1012)

			Cells Scored	Not Computed TG	Not Computed SG	Simple TB	Simple SB	Complex TI	Complex TR	Complex QR	Complex CR	Complex D	Complex R	Complex CI	Complex DF	Other GT	# of Aberrations per Cell	% Cells with Aberrations	% Cells with >1 Aberrations	% Polyploid Cells	% Endoreduplicated Cells	% Mitotic Index
CONTROLS																						
NEGATIVE:	RPMI 1640		A 100	1													0.00	0.0	0.0	0.0	0.0	1.6
			B 100		1												0.00	0.0	0.0	1.0	0.0	2.7
			A+B 200	1	1												0.00	0.0	0.0	0.5	0.0	2.2
SOLVENT:	Water	50.0 µl/ml	A 100	1													0.00	0.0	0.0	0.0	0.0	2.3
			B 100	2			1										0.01	1.0	0.0	0.0	0.0	2.1
			A+B 200	3			1										0.01	0.5	0.0	0.0	0.0	2.2
TEST ARTICLE		15.4 µg/ml*	A+B 0																			3.2
		26.8 µg/ml	A 100	3	1												0.00	0.0	0.0	0.0	0.0	2.4
			B 100	4													0.00	0.0	0.0	0.0	0.0	1.8
			A+B 200	7	1												0.00	0.0	0.0	0.0	0.0	2.1
		87.5 µg/ml*	A+B 0																			1.9
		154 µg/ml*	A+B 0																			1.8
		308 µg/ml	A 100	2													0.00	0.0	0.0	1.0	0.0	1.1
			B 100	5													0.00	0.0	0.0	2.0	1.0	1.3
			A+B 200	7													0.00	0.0	0.0	1.5	0.5	1.2
		669 µg/ml	A 100	3			1										0.01	1.0	0.0	0.0	0.0	1.3
			B 100	1	3	1	1										0.05	1.0	0.0	0.0	0.0	1.2
			A+B 200	4	5	1	2										0.03	1.0	0.0	0.0	0.0	1.6
		1337 µg/ml	A 100	3													0.00	0.0	0.0	5.0	0.0	1.2
			B 100	2													0.00	0.0	0.0	0.0	0.0	1.1
			A+B 200	5													0.00	0.0	0.0	1.5	0.0	1.3
		[illegible] µg/ml	A 100		1												0.00	0.0	0.0	1.0	0.0	1.3
			B 100														0.00	0.0	0.0	0.0	0.0	1.8
			A+B 200		1												0.00	0.0	0.0	0.0	0.0	1.5
		2673 µg/ml	A 0**																			0.8
			B 125	11			4			1							0.04	4.0	0.0	0.0	0.0	0.1
			A+B 125														0.04	4.0	0.0	0.0	0.0	0.1

RPMI 1640 = Culture medium   * Not selected for analysis of chromosomal aberrations.   ** Culture not analyzable.

Figure 77, from page 19 of Report 18585-0-449OECD

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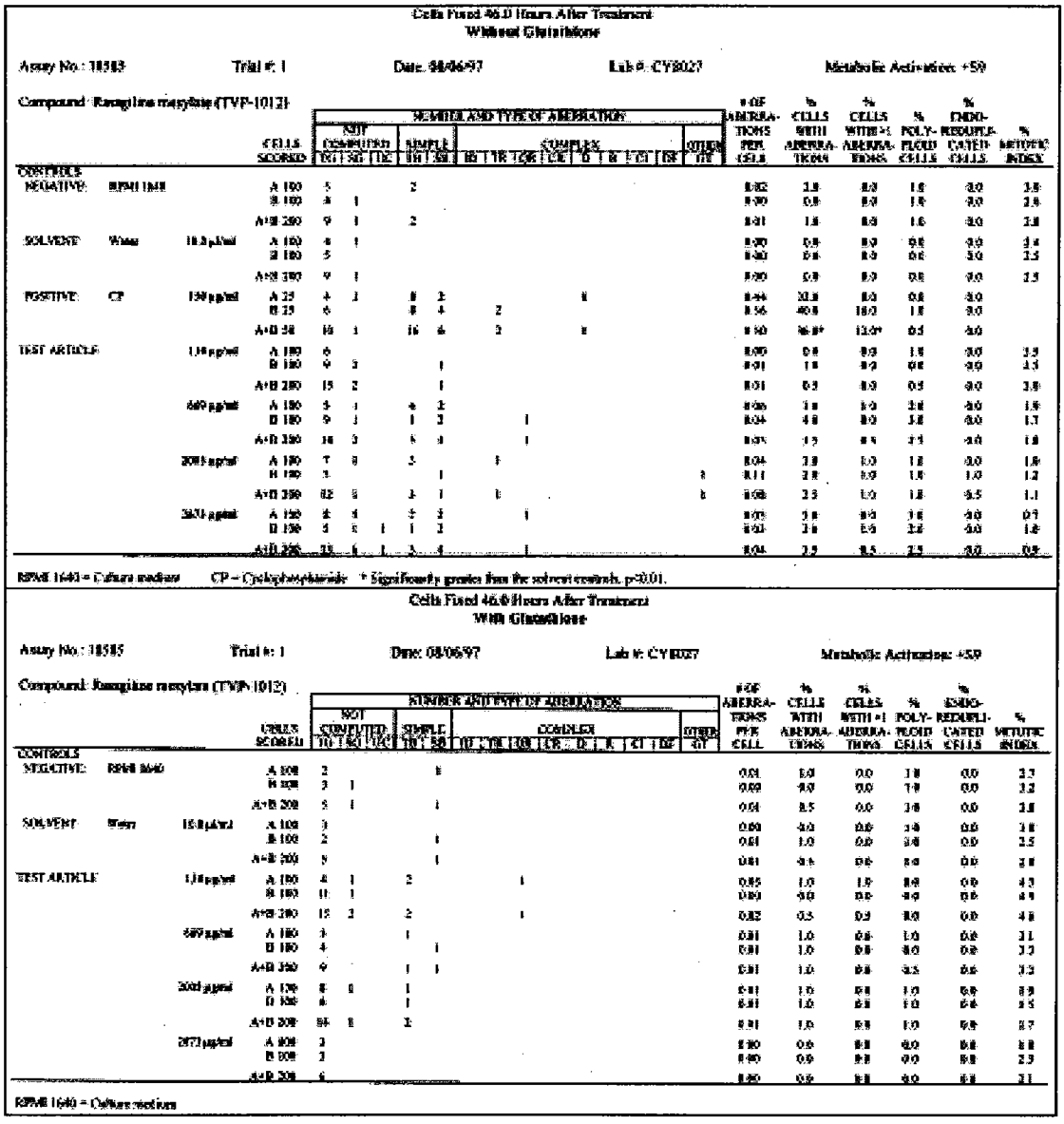

Cells Fixed 46.0 Hours After Treatment
Without Glutathione

Assay No.: 18585 Trial #: 1 Date: 08/06/97 Lab #: CYB027 Metabolic Activation: +S9

Compound: Ranolazine mesylate (TVP-1012)

				CELLS SCORED	NUMBER AND TYPE OF ABERRATION: NOT CONSTITUTED			SIMPLE		COMPLEX									OTHER	# OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS	% POLYPLOID CELLS	% ENDOREDUPLICATED CELLS	% MITOTIC INDEX
					TG	SG	TE	TB	SB	TR	TGR	TGE	D	R	CT	SE	TE							
CONTROLS																									
NEGATIVE:	RPMI 1640		A	100	5			2											0.07	3.0	0.0	1.0	0.0	3.0
			B	100	3	1													0.04	4.0	0.0	1.0	0.0	2.5
			A+B	200	8	1		2											0.05	3.5	0.0	1.0	0.0	2.8
SOLVENT:	Water	10.0 µL/ml	A	100	4	1													0.05	5.0	0.0	0.0	0.0	2.5
			B	100	5														0.05	5.0	0.0	0.0	0.0	2.5
			A+B	200	9	1													0.05	5.0	0.0	0.0	0.0	2.5
POSITIVE:	CP	150 µg/ml	A	25	4	1		8	2				1						0.44	32.0	8.0	0.0	0.0	
			B	25	6			8	4	2									0.56	40.0	16.0	1.0	0.0	
			A+B	50	10	1		16	6	2			1						0.50	36.0*	12.0*	0.5	0.0	
TEST ARTICLE:		1.56 µg/ml	A	100	6														0.06	6.0	0.0	1.0	0.0	2.5
			B	100	9	3			1										0.13	12.0	0.0	0.0	0.0	2.5
			A+B	200	15	3			1										0.10	9.0	0.0	0.5	0.0	2.5
		469 µg/ml	A	100	5	1		4	2										0.11	7.0	1.0	2.0	0.0	1.5
			B	100	9	1		1	2			1							0.14	8.0	2.0	2.0	0.0	1.7
			A+B	200	14	2		5	4			1							0.13	7.5	1.5	2.5	0.0	1.6
		2083 µg/ml	A	100	7	0		3		1								1	0.14	7.0	1.0	1.0	0.0	1.5
			B	100	3				1									1	0.11	5.0	0.0	1.0	1.0	1.2
			A+B	200	10	0		3	1	1								2	0.12	6.0	0.5	1.0	0.5	1.1
		2673 µg/ml	A	100	4	1		5	3			1							0.13	7.0	0.0	1.0	0.0	0.9
			B	100	5	1	1	1	3			1							0.12	7.0	0.0	2.0	0.0	1.0
			A+B	200	9	1	1	6	4			2							0.13	7.0	0.5	1.5	0.0	0.9

RPMI 1640 = Culture medium CP = Cyclophosphamide * Significantly greater than the solvent controls, p<0.01.

Cells Fixed 46.0 Hours After Treatment
With Glutathione

Assay No.: 18585 Trial #: 1 Date: 08/06/97 Lab #: CYB027 Metabolic Activation: +S9

Compound: Ranolazine mesylate (TVP-1012)

				CELLS SCORED	NUMBER AND TYPE OF ABERRATION: NOT CONSTITUTED			SIMPLE		COMPLEX									OTHER	# OF ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	% CELLS WITH >1 ABERRATIONS	% POLYPLOID CELLS	% ENDOREDUPLICATED CELLS	% MITOTIC INDEX
					TG	SG	TE	TB	SB	TR	TGR	TGE	D	R	CT	SE	TE							
CONTROLS																									
NEGATIVE:	RPMI 1640		A	100	2				1										0.01	1.0	0.0	1.0	0.0	2.7
			B	100	3	1													0.04	4.0	0.0	1.0	0.0	3.2
			A+B	200	5	1			1										0.03	2.5	0.0	1.0	0.0	2.8
SOLVENT:	Water	10.0 µL/ml	A	100	3														0.03	3.0	0.0	1.0	0.0	1.8
			B	100	2				1										0.04	3.0	0.0	2.0	0.0	2.5
			A+B	200	5				1										0.04	3.0	0.0	1.5	0.0	2.2
TEST ARTICLE:		1.56 µg/ml	A	100	4	1		2				1							0.05	3.0	1.0	1.0	0.0	4.3
			B	100	11	1													0.04	4.0	0.0	4.0	0.0	4.9
			A+B	200	15	2		2				1							0.04	3.5	0.5	2.5	0.0	4.6
		469 µg/ml	A	100	3			1											0.04	1.0	0.0	1.0	0.0	3.1
			B	100	4				1										0.04	1.0	0.0	2.0	0.0	3.2
			A+B	200	9			1	1										0.04	1.0	0.0	1.5	0.0	3.2
		2083 µg/ml	A	100	8	1		1											0.04	1.0	0.0	1.0	0.0	3.9
			B	100	6			1											0.04	1.0	0.0	1.0	0.0	3.5
			A+B	200	14	1		2											0.04	1.0	0.0	1.0	0.0	3.7
		2673 µg/ml	A	100	3														0.03	3.0	0.0	0.0	0.0	3.8
			B	100	3														0.03	3.0	0.0	0.0	0.0	2.3
			A+B	200	6														0.03	3.0	0.0	0.0	0.0	3.1

RPMI 1640 = Culture medium

Figure 79, from page 21 of Report 18585-0-449OECD

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3.4.4.6 STUDY TO EVALUATE THE CHROMOSOME DAMAGING POTENTIAL OF TVP-101 BY ITS EFFECTS ON CULTURED HUMAN PERIPHERAL BLOOD LYMPHOCYTES USING AN IN VITRO CYTOGENETICS ASSAY

Key findings:
Rasagiline induced a significant increase in the incidence of chromosomal aberrations in the presence of metabolic activation. There was also an increase at the middose, but not the low or high dose in the absence of metabolic activation.

Study no.: 1 ΓIP.002 TIP 2/

Location: /tox/1 .E TIP 002TIP2 ρdf
Conducting laboratory and location:
Date of study initiation: November 4,1992
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: RLB 91400530,

Methods

Strains/species/cell line:
Human Peripheral Lymphocytes

Doses used in definitive study:
See below

Basis of dose selection:
50-80% decrease in Mitotic Index in Dose Range Finding Study.

Negative controls:
Vehicle (water)

Positive controls:
4-Nitroquinoline 1-oxide (1.25, 2.5, 5.0 ug/ml) -S9
Cyclophosphamide (12.5, 25 ug/ml) +S9

Metabolic Activation System:
Aroclor 1254 pretreated male rat hepatic S9 (dosage and duration not given). Media contrained 5% of S9 mixture.

Incubation and sampling times:
-S9- 20 hour incubation (trial 1)
-S9- 44 hour incubation (trial 1) [not evaluated]
+S9- 3 hour incubation with 17 hour recovery (trial 1)
+S9- 3 hour incubation with 41 hour recovery (trial 2) [not evaluated]

Results

Study validity (comment on replicates, criteria for positive results, etc.):
The methods were appropriate. The positive and negative controls gave appropriate responses. The study is considered valid.

Study outcome:
Rasagiline caused an increase in the incidence of chromosomal aberrations starting at the lowest dose tested (1168 ug/ml) in the presence of metabolic activation. In addition, an increase was observed at 492.9 ug/ml in the absence of metabolic activation, but not at 657.2 ug/ml. Due to the positive result in the first study, the other planed studies were not conducted.

Incidence of Aberrations in the Absence of Metabolic Activation after 20 hours of Treatment

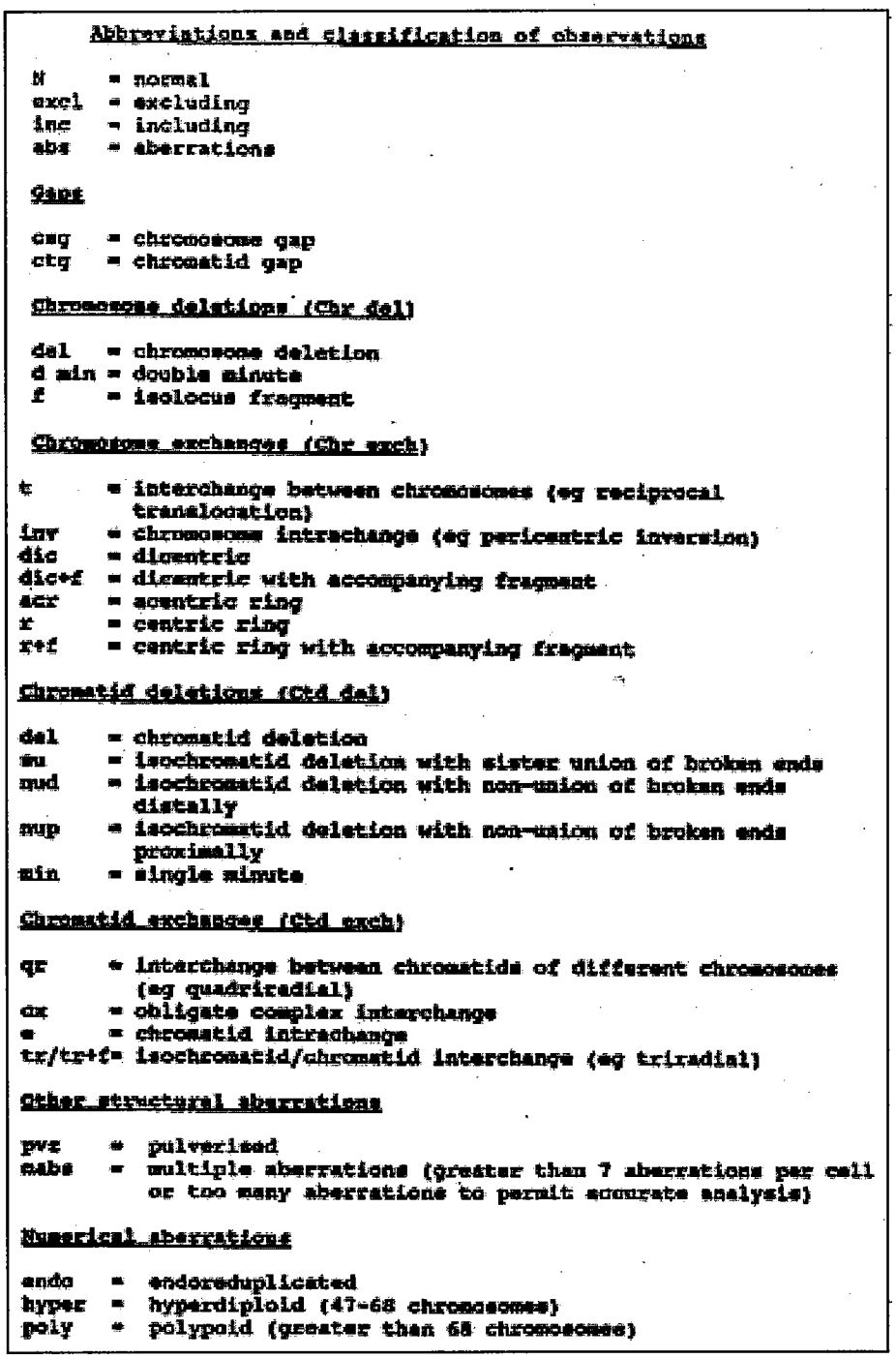
Dose ug/ml	Cell	Gap	Chr del	Chr exch	Ctd del	Ctd exch	Other	Abs +gap	Abs -gap (%Abs)	Num Abs	MI
0	200	3	0	0	3	0	0	6	3 (1.5)	0	6.0
369.7	200	11	1	0	5	0	0	15	6 (3.0)	1	3.6
492.9	200	12	0	0	9	1	0	20	*10 (5.0)*	3	2.9
657.2	179	9	0	0	4	0	0	10	4 (2.2)	0	2.5
NQO	50	5	0	0	14	8	1	15	***14 (28.0)***	0	

Abs refers to number of cells with aberrations (cells may have more than one type of aberration).
Values in *Italics* were statistically significant ($p \leq 0.05$)

Incidence of Aberrations in the Presence of Metabolic Activation after 3 hours of Treatment followed by17 hours of Recovery

Dose ug/ml	Cell	Gap	Chr del	Chr exch	Ctd del	Ctd exch	Other	Abs +gap	Abs -gap (%Abs)	Num Abs	MI
0	200	5	2	0	2	0	0	9	4 (2.0)	0	6.2
1168	200	12	4	1	9	1	1	21	**15 (7.5)**	13	2.7
1558	200	17	9	0	20	3	2	35	***27 (13.5)***	6	2.6
2077	200	20	4	0	29	3	0	30	***22 (11.0)***	11	2.9
CPA	50	6	11	0	22	1	0	25	***24 (48.0)***	0	--

Abs refers to number of cells with aberrations (cells may have more than one type of aberration).
Values in **Bold** were statistically significant ($p \leq 0.01$)
Values in ***Bold Italic*** were statistically significant ($p \leq 0.001$)



Abbreviations and classification of observations

N = normal
excl = excluding
inc = including
abs = aberrations

Gaps

csg = chromosome gap
ctg = chromatid gap

Chromosome deletions (Chr del)

del = chromosome deletion
d min = double minute
f = isolocus fragment

Chromosome exchanges (Chr exch)

t = interchange between chromosomes (eg reciprocal translocation)
inv = chromosome intrachange (eg pericentric inversion)
dic = dicentric
dic+f = dicentric with accompanying fragment
acr = acentric ring
r = centric ring
r+f = centric ring with accompanying fragment

Chromatid deletions (Ctd del)

del = chromatid deletion
su = isochromatid deletion with sister union of broken ends
mud = isochromatid deletion with non-union of broken ends distally
mup = isochromatid deletion with non-union of broken ends proximally
min = single minute

Chromatid exchanges (Ctd exch)

qr = interchange between chromatids of different chromosomes (eg quadriradial)
cx = obligate complex interchange
e = chromatid intrachange
tr/tr+f= isochromatid/chromatid interchange (eg triradial)

Other structural aberrations

pvz = pulverised
mabs = multiple aberrations (greater than 7 aberrations per cell or too many aberrations to permit accurate analysis)

Numerical aberrations

endo = endoreduplicated
hyper = hyperdiploid (47-68 chromosomes)
poly = polypoid (greater than 68 chromosomes)

Figure 80, from page 24 of Report 1 *E*TIP.002 TIP *2*

3.4.4.7 CYTOTOXICITY AND MUTAGENICITY TEST ON RASAGILINE MESYLATE (TVP-1012) IN THE L5178Y TK+/- MOUSE LYMPHOMA FORWARD MUTATION ASSAY WITH AND WITHOUT METABOLIC ACTIVATION AND IN THE PRESENCE OF 1 MM GLUTATHIONE UNDER ACTIVATION CONDITIONS

Key findings:
Rasagiline was positive in this assay in the presence and absence of metabolic activation. Colony sizing showed that there was an increase in small colonies suggesting that the effect was due to clastogenesis. Rasagiline was positive in the presence of glutathione.

Study no.: 18585-0-431CY and 18585-1-431

Location: /tox/18585-0-431CY and 18585-1-431.pdf
Conducting laboratory and location:
Date of study initiation: July 29, 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: CN:255495223

Methods

Strains/species/cell line:
L5178Y TK+/- Mouse Lymphoma Cells

Doses used in definitive study:

Basis of dose selection:
10-20% survival compared to control in range finding assay

Negative controls:
Vehicle (water)

Positive controls:
-S9: Methyl methanesulfonate- 5, 10 nl/ml
+S9: Methylcholanthrene- 2, 4 ug/ml

Metabolic Activation System:
Hepatic S9 from male rats pretreated with 500 mg/kg/day Aroclor 1254 for 5 days. Concentration in the test media was not given.

Incubation and sampling times:
4 hour incubation with rasagiline followed by 48 hour expression period.

Results

Study validity (comment on replicates, criteria for positive results, etc.):
Appropriate methods were used. The positive and negative controls gave the expected results. The study is considered valid.

Study outcome:
Rasagiline increased the incidence of mutations in the absence of metabolic activation at 1000 ug/ml and in the presence of metabolic activation at 0.25 and 5 ug/ml (although not at the three intermediate doses). The addition of 1 mM glutathione reduced the cytotoxicity of rasagiline (enabling higher doses to be tested), but the higher doses were also mutagenic (50, 75, 100 ug/ml). Colony sizing suggested that there was an increase in the proportion of small colonies suggesting that rasagiline is clastogenic.

MUTATION ASSAY WITHOUT ACTIVATION

A. TEST ARTICLE: RASAGILINE MESYLATE (TVP-1012)
B. GENETICS ASSAY NO: 18585
C. VEHICLE: TISSUE CULTURE WATER
D. SELECTIVE AGENT: 3 µg/ml
E. TEST DATE: 09/23/97

TEST CONDITION	DAILY CELL COUNTS (CELLS/ML.10E5 UNITS) 1	2	SUSPENSION GROWTH[1]		TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY[2]		RELATIVE GROWTH (%)[3]	MUTANT FREQUENCY (10E-6 UNITS)[4]
NONACTIVATION CONTROLS[5]			AVG VEHICLE CONTROL				AVG VEHICLE CONTROL			
VEHICLE CONTROL	17.3	11.3	21.7		123	344	57.3		100.0	71.5
VEHICLE CONTROL	19.5	9.3	22.2		170	523	87.2		100.0	65.0
VEHICLE CONTROL	18.8	8.9	18.6	20.7	173	556	92.7	79.1	100.0	44.2
MMS 5 ul/ml	8.7	15.6	13.1		448	461	76.8		63.0	194.4[7]
MMS 10 ul/ml	9.9	9.5	10.5		497	304	50.7		33.3	327.0[7]
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)				RELATIVE TO VEHICLE CONTROL (%)			
200 µg/ml	14.0	11.6	89.3		122	540	113.8		101.6	46.2
400 µg/ml	14.5	11.4	93.9		118	458	96.5		87.7	51.5
500 µg/ml	10.7	13.1	65.3		130	562	118.4		77.3	46.3
600 µg/ml	8.5	13.1	61.2		169	588	123.9		75.8	57.5
800 µg/ml	9.2	12.1	61.2		139	500	105.4		64.5	55.6
1000 µg/ml	2.4*	13.3	21.9		275	438	92.3		20.2	125.6[7]

[1]SUSPENSION GROWTH = (DAY 1 COUNT/3) * (DAY 2 COUNT)/13 OR DAY 1 COUNT IF NOT SPLIT BACK)

[2]CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

[3]RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

[4]MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4 DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

[5]VEHICLE CONTROL = 10% TISSUE CULTURE WATER; MMS = METHYL METHANESULFONATE POSITIVE CONTROL

[7]MUTAGENIC, EXCEEDS MINIMUM CRITERION OF 120.5 X 10E-6

* NOT SPLIT BACK

Figure 81, from page 30 of Report 18585-0-431CY and 18585-1-431

MUTATION ASSAY WITH S9 ACTIVATION

A. TEST ARTICLE: RASAGILINE MESYLATE (TVP-1012)
B. GENETICS ASSAY NO: 18585
C. VEHICLE: TISSUE CULTURE WATER
D. SELECTIVE AGENT: TFT 3.0 µg/ml
E. TEST DATE: 09/23/97

TEST CONDITION*	DAILY CELL COUNTS (CELLS/ML..1E5 UNITS) 1	2	SUSPENSION GROWTH*		TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*		RELATIVE GROWTH (%)*	MUTANT FREQUENCY (10E-6 UNITS)*
S9 ACTIVATION CONTROLS* S9 BATCH NO:0755			AVG VEHICLE CONTROL					AVG VEHICLE CONTROL		
VEHICLE CONTROL	18.3	9.2	18.7		159	593	98.8		100.0	53.6
VEHICLE CONTROL	15.7	11.7	20.4		161	545	90.8		100.0	59.1
VEHICLE CONTROL	18.8	8.3	17.3	18.8	152	562	93.7	94.4	100.0	54.1
MCA 2 µg/ml	8.9	9.1	9.0		736	406	67.7		24.3	362.5*
MCA 4 µg/ml	8.1	8.1	7.3		770	362	60.3		24.8	425.4*
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)				RELATIVE TO VEHICLE CONTROL (%)			
0.250 µg/ml	17.1	10.8	109.1		251	433	76.4		83.4	116.9*
0.500 µg/ml	17.9	11.0	116.4		180	438	77.3		90.0	82.2
1.00 µg/ml	15.5	10.9	99.9		189	583	102.9		102.8	64.8
2.50 µg/ml	11.3	10.8	72.1		243	480	84.7		61.1	101.3
5.00 µg/ml	6.0	7.7	27.3		537	572	101.0		27.6	186.0*

*SUSPENSION GROWTH = (DAY 1 COUNT/31 * (DAY 2 COUNT)/13 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% TISSUE CULTURE WATER. MCA = METHYLCHOLANTHRENE.POSITIVE CONTROL

*MUTAGENIC: EXCEEDS MINIMUM CRITERION OF 115.2 X 10E-6

Figure 82, from page 31 of Report 18585-0-431CY and 18585-1-431

APPEARS THIS WAY
ON ORIGINAL

MUTATION ASSAY WITH S9 ACTIVATION AND GLUTATHIONE

A. TEST ARTICLE: RASAGILINE MESYLATE (TVP-1012)
B. GENETICS ASSAY NO: 18585
C. VEHICLE: TISSUE CULTURE WATER
D. SELECTIVE AGENT: TFT 3.0 µg/ml
F. TEST DATE: 09/25/97

TEST CONDITION	DAILY CELL COUNTS (CELLS/ML, 10E5 UNITS) 1	2	SUSPENSION GROWTH*		TOTAL MUTANT COLONIES	TOTAL VIABLE COLONIES	CLONING EFFICIENCY*		RELATIVE GROWTH (%)*		MUTANT FREQUENCY (10E-6 UNITS)*
S9 ACTIVATION CONTROLS*	S9 BATCH NO: 0766		AVG VEHICLE CONTROL					AVG VEHICLE CONTROL			
VEHICLE CONTROL	22.3	9.5	23.5		133	537	89.5		100.0		49.5
VEHICLE CONTROL	21.0	9.9	23.1		193	602	100.3		100.0		64.1
VEHICLE CONTROL	19.5	9.7	21.0	22.5	214	564	94.0	94.6	100.0		75.9
MCA 2 µg/ml	17.8	9.1	18.0		558	628	104.7		88.5		177.7#
MCA 4 µg/ml	17.9	10.3	20.5		622	408	68.0		66.5		304.9#
TEST COMPOUND			RELATIVE TO VEHICLE CONTROL (%)				RELATIVE TO VEHICLE CONTROL (%)				
10.0 µg/ml	15.3	9.7	73.3		199	508	89.5		65.5		78.3
25.0 µg/ml	14.9	10.3	85.1		211	453	79.8		56.3		93.2
50.0 µg/ml	9.4	6.5	39.5		405	376	66.2		25.1		215.4#
75.0 µg/ml	6.7	5.7	28.8		403	314	55.3		15.9		256.7#
100 µg/ml	2.8*	5.6	8.3		572	352	62.0		5.1		325.0#

*SUSPENSION GROWTH = (DAY 1 COUNT/3) + (DAY 2 COUNT)/(3 OR DAY 1 COUNT IF NOT SPLIT BACK)

*CLONING EFFICIENCY = TOTAL VIABLE COLONY COUNT/NUMBER OF CELLS SEEDED * 100

*RELATIVE GROWTH = (RELATIVE SUSPENSION GROWTH * RELATIVE CLONING EFFICIENCY) / 100

*MUTANT FREQUENCY = (TOTAL MUTANT COLONIES/TOTAL VIABLE COLONIES) X 2X10E-4. DECIMAL IS MOVED TO EXPRESS THE FREQUENCY IN UNITS OF 10E-6

*VEHICLE CONTROL = 10% TISSUE CULTURE WATER; MCA = METHYLCHOLANTHRENE POSITIVE CONTROL

#MUTAGENIC. EXCEEDS MINIMUM CRITERION OF 126.3 X 10E-6

* NOT SPLIT BACK

Figure 83, from page 32 of Report 18585-0-431CY and 18585-1-431

APPEARS THIS WAY
ON ORIGINAL

ANALYSIS OF COLONY SIZE WITH RASAGILINE MESYLATE (TVP-1012)
— ASSAY NUMBER 18585-1-431

Dose (µg/ml)		S9	Mutant Frequency (x 10^{-6})*	% Large Colonies	% Small Colonies	Ratio S/L*
Trial 1						
VC[b]		-	50.9	49.0	51.0	1.04
PC[c]		-	331.3	49.8	50.2	1.01
1000		-	123.3	46.3	53.7	1.16
VC[b]	without glutathione	+	50.0	53.4	46.6	0.87
PC[d]		+	416.7	38.9	61.1	1.57
5.00		+	175.0	43.0	57.0	1.33
VC[b]	with glutathione	+	60.3	48.8	51.2	1.05
PC[d]		+	286.0	40.7	59.3	1.46
75.0		+	248.3	20.3	79.7	3.94

[a]ratio of small colonies to large colonies
VC[b]= vehicle control
PC[c]= methyl methanesulfonate (10 nl/ml)
PC[d]= methylcholanthrene (4 µg/ml)

Entire plate cannot be sized due to interference from sides of plate. Mutant frequencies will therefore appear different from Tables 2 through 4 .

Figure 84, from page 33 of Report 18585-0-431CY and 18585-1-431

Estimated Mutation Frequencies (x 10^{-6}) derived from Figure 84

Dose	Glutathione	S9	Total MF	Large Colony MF	Small colony MF
VC	-	-	50.9	24.9	26.0
PC	-	-	331.3	165.0	166.3
1000	-	-	123.3	46.3	66.2
VC	-	+	50.0	26.7	23.3
PC	-	+	416.7	162.1	254.6
5.0	-	+	175.0	75.3	99.8
VC	+	+	60.3	29.4	30.9
PC	+	+	286.0	116.4	169.6
75.0	+	+	248.3	50.4	197.9

3.4.4.8 TVP-1012 MOUSE MICRONUCLEUS TEST

Key findings:
Rasagiline did not increase the incidence of micronuclei in this study.

Study no.: M/MMN/35197

Location: /tox/MMMN35197.pdf
Conducting laboratory and location: [redacted]
Date of study initiation: about July 1992
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: P.92208

Methods

Strains/species/cell line:
Mouse, CD-1

Doses used in definitive study:
50, 100, 200 mg/kg, PO

Basis of dose selection:
Mortality in dose range finding study at 320 mg/kg

Negative controls:
Vehicle (water)

Positive controls:
Mitomycin C, 4 mg/kg ip

Incubation and sampling times:
Mice were given single PO dose of rasagiline and sacrificed 24, 48, 72 hours post injection. Five mice/sex/dose were used at each time point.

Results

Study validity (comment on replicates, criteria for positive results, etc.):
Positive and negative controls had appropriate responses. The high dose was adequate based on mortality at 320 mg/kg.

Study outcome:
Rasagiline was negative in this assay.

Males

Day	Dose	Mean PCE	Mean MN-PCE	Mean MN-NCE	Ratio PCE/NCE	Mean % MN-PCE
1	0	1011.6	0.4	0.0	1.02	0.04
	50	1093.0	0.4	0.2	1.01	0.04
	100	1020.0	0.4	0.2	1.03	0.04
	200	1047.6	0.2	0.2	0.92	0.02
	PC	1054.6	12.4	1.0	0.86	1.17
2	0	1021.4	0.0	0.2	1.01	0.00
	50	1022.4	0.0	0.0	0.97	0.00
	100	1005.6	0.0	0.2	0.92	0.00
	200	1020.8	0.2	0.0	0.99	0.02
3	0	1024.6	0.0	0.2	0.95	0.00
	50	1010.0	0.0	0.2	0.98	0.00
	100	1021.6	0.0	0.0	1.00	0.00
	200	1030.8	0.6	0.4	0.95	0.06

Females

Day	Dose	Mean PCE	Mean MN-PCE	Mean MN-NCE	Ratio PCE/NCE	Mean % MN-PCE
1	0	1006.6	0.4	0.2	0.95	0.04
	50	1035.2	0.4	0.4	0.99	0.04
	100	1023.6	0.2	0.0	1.03	0.02
	200	1018.6	0.0	0.0	0.94	0.00
	PC	1030.8	13.0	0.8	0.95	1.26
2	0	1024.6	0.2	0.2	1.01	0.02
	50	1012.4	0.0	0.0	1.00	0.00
	100	1014.0	0.0	0.0	0.98	0.00
	200	1022.0	0.0	0.0	1.01	0.00
3	0	1043.6	0.2	0.2	0.94	0.02
	50	1019.6	0.0	0.2	1.00	0.00
	100	1011.0	0.2	0.0	0.99	0.02
	200	1018.8	0.0	0.0	0.99	0.00

Combined Sexes

Day	Dose	Mean PCE	Mean MN-PCE	Mean MN-NCE	Ratio PCE/NCE	Mean % MN-PCE
1	0	1010.1	0.4	0.1	0.99	0.04
	50	1064.1	0.4	0.3	1.00	0.04
	100	1021.8	0.3	0.1	1.03	0.03
	200	1033.1	0.1	0.1	0.93	0.01
	PC	1030.8	13.0	0.8	0.95	1.26
2	0	1023.0	0.1	0.2	1.01	0.01
	50	1017.4	0.0	0.0	0.98	0.00
	100	1009.8	0.0	0.1	0.95	0.00
	200	1021.4	0.1	0.0	1.00	0.01
3	0	1034.1	0.1	0.2	0.95	0.01
	50	1014.8	0.0	0.1	0.99	0.00
	100	1016.3	0.1	0.0	1.00	0.01
	200	1024.8	0.3	0.2	0.97	0.03

3.4.4.9 GENOTOXICITY TEST ON THE EFFECT OF RASAGILINE MESYLATE (TVP-1012) ON IN VIVO/IN VITRO UNSCHEDULED DNA SYNTHESIS IN RAT PRIMARY HEPATOCYTE CULTURES AT TWO TIMEPOINTS

Key findings:
Rasagiline did not induce unscheduled DNA synthesis in this study..

Study no.: 18585-0-494

Location: /tox/18585-0-494.pdf
Conducting laboratory and location: —
Date of study initiation: June 3, 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: CN:255495223

Methods

Strains/species/cell line:
Rat, International Gold Standard – CD(SD)IGS BR), males only

Doses used in definitive study:
25, 50, 100, 200 mg/kg, PO

Basis of dose selection:
Maximum tolerated dose

Negative controls:
Vehicle (water)

Positive controls:
N-Dimethylnitrosamine 10 mg/kg ip (2-3 hour timepoint), 15 mg/kg ip (15-16 hour timepoint)

Incubation and sampling times:
Rats were given single dose of rasagiline and sacrificed 2-3 hours or 15-16 hours later. Hepatocytes were isolated and examined for unscheduled DNA synthesis using tritiated thymidine. Three rats were used per timepoint.

Results

Study validity (comment on replicates, criteria for positive results, etc.):
Positive and negative controls had appropriate responses. The high dose was adequate based on mortality observed at 200 mg/kg in this study.

Study outcome:
Rasagiline was negative in this assay. Two out of three rats died prior to sacrificed at the 15-16 hour time point. The 200 mg/kg group could not be analyzed due to this toxicity.

Table 3. Summary of UDS at the 2- to 3-hour Timepoint

Dose Level mg/kg	Mean Net Nuclear Grain Count*	% Cells with ≥ 5 Mean Net Nuclear Grains*	Mean Cytoplasmic grain count*
Vehicle Control	-0.82	2.00	6.02
Positive Control DMN 10.00	23.22	96.84	7.25
200	-0.95	2.00	5.83
100	-1.65	0.89	5.51
50.0	-0.96	0.89	5.03

* The group means are grand means, calculated based on the actual grain counts and weighted for the actual number of cells analyzed per slide.

Figure 85, from page 21 of Report 18585-0-494

Table 4. Summary of UDS at the 15- to 16-hour Timepoint

Dose Level mg/kg	Mean Net Nuclear Grain Count*	% Cells with ≥ 5 Mean Net Nuclear Grains*	Mean Cytoplasmic grain count*
Vehicle Control	-0.97	1.11	4.26
Positive Control DMN 15.00	8.95	66.00	6.19
100	-0.95	0.33	3.45
50.0	-1.03	0.40	4.13
25.0	-1.16	2.22	5.88

* The group means are grand means, calculated based on the actual grain counts and weighted for the actual number of cells analyzed per slide.

Figure 86, from page 22 of Report 18585-0-494

3.4.4.10 *IN VIVO* MOUSE MICRONUCLEUS ASSAY WITH RASAGILINE MESYLATE IN COMBINATION WITH 80 MG/KG/20 MG/KG LEVODOPA/CARBIDOPA & LEVODOPA/CARBIDOPA ALONE USING THE ORAL GAVAGE ROUTE OF ADMINISTRATION

Key findings:
Rasagiline mesylate in combination with 80 mg/kg/20 mg/kg Levodopa/Carbidopa & Levodopa/Carbidopa alone, was negative in the mouse bone marrow micronucleus assay under the conditions of this assay.

Study no.: 21326-0-455OECD

Location: /tox/21326-0-455OECD.pdf
Conducting laboratory and location:
Date of study initiation: March 22, 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: CN: 255400199

Methods

Strains/species/cell line:
Mice, Crl:CD-1 (ICR) BR strain, males

Doses used in definitive study:
See below.

Basis of dose selection:
5/6 mice dosed with 200 mg/kg rasagiline with 80/20 mg/kg levodopa/carbidopa died within 24 hours of treatment. No mortality was noted with the combination of 100 mg/kg rasagiline with 80/20 mg/kg levodopa/carbidopa.

Negative controls:
Vehicle (water)

Positive controls:
Cyclophosphamide

Incubation and sampling times:
24 and 48 hours post dose

Results

Study validity (comment on replicates, criteria for positive results, etc.):
Positive and negative controls had appropriate responses.

Study outcome:
No significant increase in micronucleus formation was observed in rasagiline treated mice.

TEST ARTICLE: Rasagiline mesylate in combination with 80 mg/kg/20 mg/kg Levodopa/Carbidopa and Levodopa/Carbidopa alone

TREATMENT	DOSE	HARVEST TIME (HR)	% MICRONUCLEATED PCEs MEAN OF 2000 PER ANIMAL ± S.E. MALES	RATIO PCE:NCE MEAN ± S.E. MALES
CONTROLS				
VEHICLE	0.5% MC	24 hr	0.02 ± 0.01	0.61 ± 0.03
		48 hr	0.02 ± 0.01	0.64 ± 0.06
LEVODOPA/CARBIDOPA	1400/350 mg/kg	24 hr	0.04 ± 0.02	0.69 ± 0.07
	2800/500 mg/kg	24 hr	0.06 ± 0.03	0.59 ± 0.06
		48 hr	0.08 ± 0.03	0.51 ± 0.05
POSITIVE	CP 80 mg/kg	24 hr	1.98 ± 0.19*	0.48 ± 0.03**
TEST ARTICLE	25.0 mg/kg	24 hr	0.03 ± 0.01	0.50 ± 0.04
	50.0 mg/kg	24 hr	0.01 ± 0.01	0.68 ± 0.06
	100 mg/kg	24 hr	0.03 ± 0.02	0.55 ± 0.04
		48 hr	0.04 ± 0.02	0.46 ± 0.06

* Significantly greater than the corresponding vehicle control, p<0.01.
** Significantly less than the corresponding vehicle control, p≤0.05.
0.5% MC = 0.5% Methylcellulose
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte

Figure 87, from page 21 of Report 21326-0-455OECD

3.4.5. Carcinogenicity

3.4.5.1 RASAGILINE MESYLATE (TVP-1012) CARCINOGENICITY STUDY BY ORAL GAVAGE ADMINISTRATION TO CD-1 MICE FOR 104 WEEKS

Key study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:
1. There was adequate survival to permit tumor development.
2. Body weights at all dose levels wee within 10% of control values.
3. No dose limiting histopathology was observed.
4. Based on the increased incidence of lung neoplasms in males, the doses in males are considered adequate.
5. An MTD was not reached in females.

Evaluation of tumor findings:
An increased incidence of combined lung adenomas/carcinoma in male mice at 45 mg/kg; there was also a significant trend in combined lung adenoma/carcinoma in male mice. Increased incidence of combined lung adenoma/carcinoma was observed in female mice, but the increase was not considered statistically significant. No other significant associations were observed in male or female mice.

Study no.: 6751-104
Location: tox\6751-104.pdf
Conducting laboratory and location: —
Date of study initiation: April 22, 1998
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity:

Control Number	Date Received	Weeks Used	Purity
255495223	13 October 1997	1 through 22	
255495223	5 June 1998	23 through 49	
255495223	26 February 1999	49 through 53	
255400199	14 April 1999	54 through 58	
255400199	21 April 1999	59 through 105	

Note: Purity results were obtained by titration assays.

Figure 88, from page 18 of Report 6751-104

CAC concurrence: The CAC (March 10, 1998) concurred with the sponsor's original doses of 1, 15 and 45 mg/kg; The committee recommended that the sponsor consider raising the low dose to enable a better evaluation of potential dose response relationships. Meeting minutes did not discuss histopathology only being done at control and high dose.

Methods

Doses: 0, 1, 15, 45 mg/kg/day
Basis of dose selection (MTD, MFD, AUC etc.): MTD
Species/strain: Mouse, CD-1(ICR)BR
Number/sex/group (main study): 55/sex/dose
Route, formulation, volume: Oral gavage, Distilled water, 5 ml/kg
Frequency of dosing: 1X/day
Satellite groups used for toxicokinetics: 50/sex/dose (rasagiline treated mice)
Satellite groups used for liver assay: 15/sex/dose (reviewed on page 14)
Satellite groups used for prolactin assay: 12/sex/dose
Age: 6 weeks at start of study
Animal housing: Individual in wire mesh cages
Restriction paradigm for dietary restriction studies: N/A
Drug stability/homogeneity: Drug formulations were stable
Dual controls employed: No
Interim sacrifices: None
Deviations from original study protocol: No significant deviations

Observation times

Mortality: 2X/day
Clinical signs: 2X/week
Body weights: 1X/week (weeks 1-14), 1X/4weeks (weeks 15-104)
Food consumption: 1X/week (weeks 1-14), 1X/4weeks (weeks 15-104)
Histopathology: Peer review: yes (X), no ( ); complete histopathology in control and high dose mice and early decedents; also gross lesions, lungs, liver, kidney and harderian gland (males only) were examined in the low and mid dose groups.
Toxicokinetics: Day 30- 0, 0.25, 0.5, 1, 2, 4 and 8 hours post dose; Week 26- 0.25 and 2 hours postdose.

Results

Mortality: No statistically significant differences, high dose males had "nearly" significant increase in mortality.

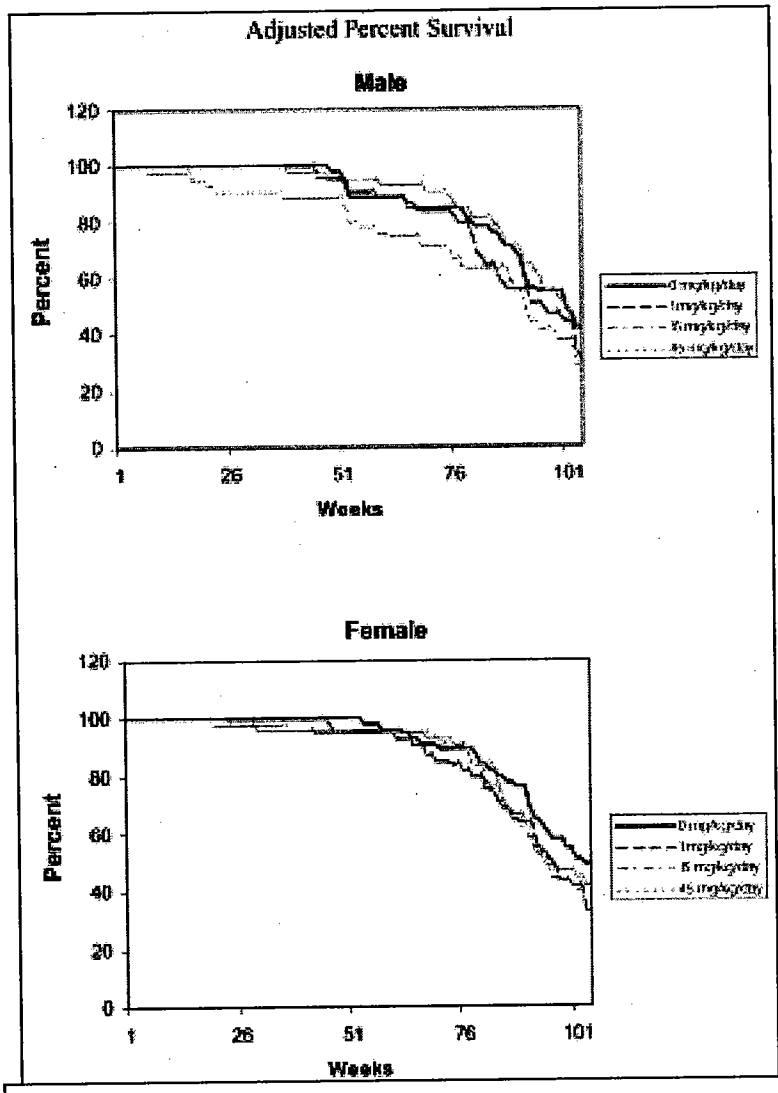


Figure 89, from page 37 of report 6751-104

Clinical signs:
Rough hair coat, yellow hair coat and yellow abdominal skin were observed in high dose males; No dose limiting clinical signs were observed

Summary of Drug-Related Clinical Observations

	Males				Females			
mg/kg/day	0	1	15	45	0	1	15	45
Hyperactivity	3	2	0	1	0	2	0	1
Rough Hair coat	13	9	9	23	20	27	25	25
Yellow Hair coat	8	7	8	24	3	0	6	3
Yellow Abdominal Skin	2	1	2	9	0	0	0	0
Swollen Ventral Abdominal region	13	10	10	16	19	12	15	9
Tremors	2	4	1	9	3	3	2	6

Incidence =Number of animals with the finding.

Figure 90, from page 38 of Report 6751-104

Body weights:
Slight decreases in body weight were observed at the high dose. The changes were about 5-6% in males and 2-8% in females. These changes would not generally be considered dose limiting.

Summary of Mean Body Weights and Weight Gains (g)

Males	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 weight gains in grams (% difference compared to Group 1 control)				
Week 1-104	13.3	13.0 (-2%)	12.5 (-6%)	11.6 (-13%)

Females	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%)
Mean body weight gains in grams (% difference compared to Group 1 control)				
Week 1-104	13.9	12.9 (-7%)	12.8 (-8%)	10.7 (-23%)*

* Mean value significantly different from control Group 1 at $p \leq 0.05$.

Figure 91, from page 39 or Report 6751-104

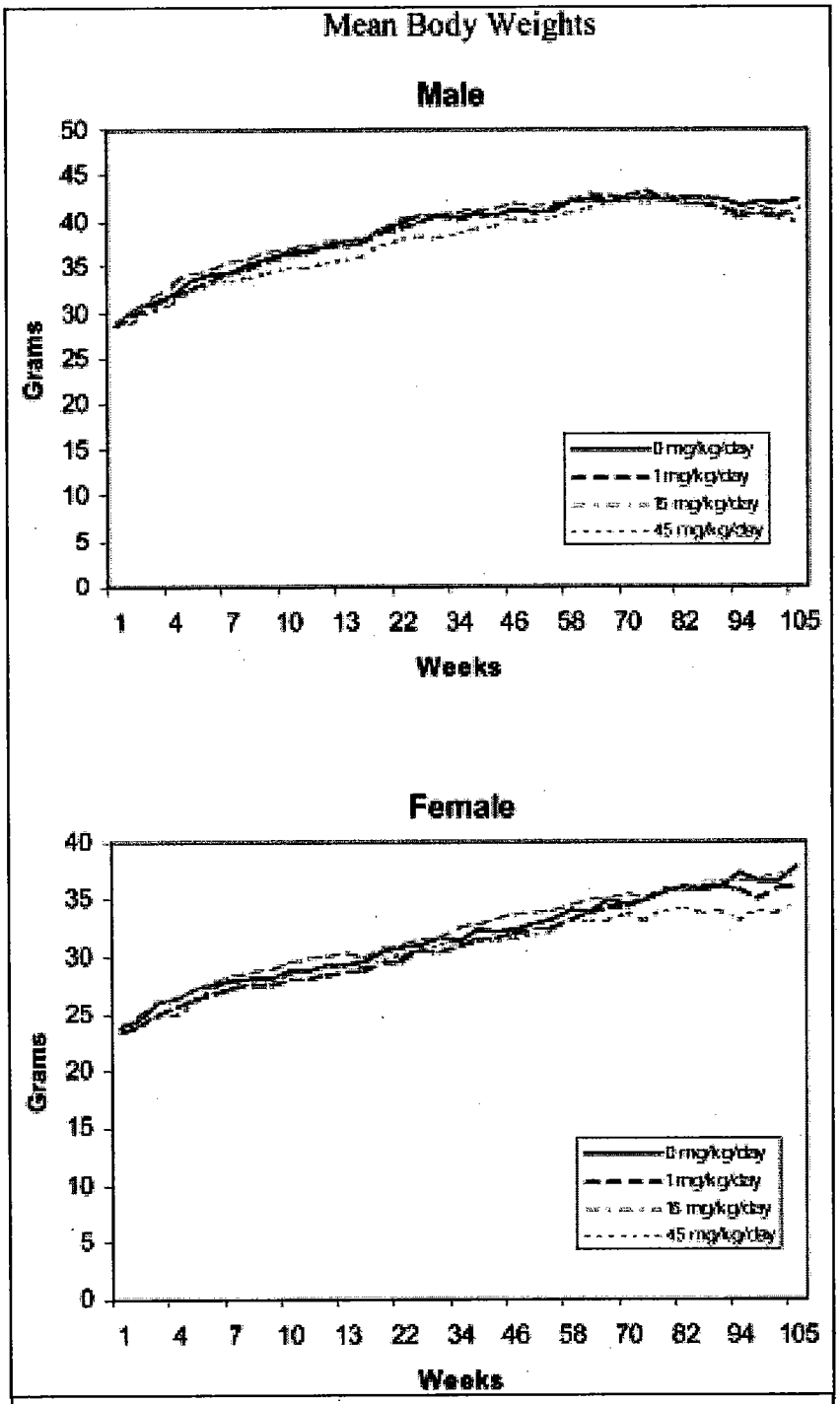


Figure 92, from page 40 of Report 6751-104

Food consumption:
Increased food consumption observed at 15 mg/kg (males only) and 45 mg/kg (both sexes.

Summary of Mean Total Food Consumption Values (g)

Males	Group 1 0 mg/kg	N	Group 2 1 mg/kg	N	Group 3 15 mg/kg	N	Group 4 45 mg/kg	N
Mean food consumptions in grams (% difference compared to Group 1 control)								
Week 1-13	461	54	468 (2%)	53	507 (10%)*	50	518(12%)*	36
Week 1-25	568	54	577 (2%)	53	639 (9%)*	46	643 (13%)*	21
Week 1-53	836	47	852 (2%)	47	893 (7%)*	36	909 (9%)*	12
Week 1-77	1069	44	1079 (1%)	34	1126 (5%)*	27	1158 (8%)*	7
Week 1-104	1333	19	1367 (3%)	14	1407 (6%)	9	1435 (8%)	2

Females	Group 1 0 mg/kg	N	Group 2 1 mg/kg	N	Group 3 15 mg/kg	N	Group 4 45 mg/kg	N
Mean food consumptions in grams (% difference compared to Group 1 control)								
Week 1-13	438	51	431 (-2%)	51	444 (1%)	54	459 (5%)*	38
Week 1-25	542	51	531 (-2%)	49	547 (1%)	52	564 (4%)*	38
Week 1-53	799	45	791 (-1%)	45	809 (1%)	42	836 (5%)*	27
Week 1-77	1028	37	1017 (-1%)	38	1044 (2%)	29	1060 (3%)	13
Week 1-104	1314	20	1265 (-4%)	14	1372 (4%)	9	1360 (4%)	4

* Mean value significantly different from control Group 1 at $p \leq 0.05$.
N=Sample size.

Figure 93, from page 43 of Report 6751-104

Hematology/Prolactin Levels:
No effects were observed on hematological parameters or on prolactin levels.

Gross pathology:
(A consolidated gross pathology table (early and terminal decedents) was not included in the study report. This was requested from the sponsor and provided in an e-mail of February 9, 2004 from Mr Dennis Williams (TEVA Neuroscience) to Ms. Teresa Wheelous (FDA))

Lung Masses

	0 mg/kg	1 mg/kg	15 mg/kg	45 mg/kg
Males	4/55	4/55	8/55	10/55
Females	2/55	3/55	7/55	10/55

Histopathology:

Non-neoplastic:

		Males				Females			
Rasagiline: mg/kg/day		0	1	15	45	0	1	15	45
Liver	#Ex	55	55	55	55	55	55	55	55
Hypertrophy		7	5	41**	49**	0	3	26**	40**
Hepatocyte, necrosis		3	1	7	35**	1	3	7*	13**
Centrilobular pigment, Lipofuscin		1	1	3	47**	2	6	7	6
Hepatocyte, karyomegaly		0	0	0	18**	0	0	0	0
Hepatocyte, increased mitotic rate		0	0	1	4	0	0	3	6*
Urinary bladder	#Ex	55	37	33	54	53	37	28	51
Dilated		8	3	10	17*	0	1	0	0

Text table data extracted from Appendix 11. #Ex = Number examined.
Statistical data extracted from Statistical Report (page 76). * = p≤0.05, ** = p≤0.01

Figure 94, from page 47 of Report 6751-104

The hepatocyte necrosis observed at 15 and 45 mg/kg was defined as "isolated, single or small clusters of necrotic hepatocytes" (page 11 of pathology report, 67 of study report). The severity was minimal to mild in all cases and was not considered of biological significance. This reviewer concurs in this assessment.

An increased incidence of cataracts was observed in males, but not females

	0 mg/kg	1 mg/kg	15 mg/kg	45 mg/kg
Males	1/46 (2.2%)	2/30 (6.7%)	1/27 (3.7%)	8/47 (17%)
Females	4/45 (8.9%)	3/34 (8.9%)	5/25 (20%)	1/34 (2.9%)

An incidence of alveolar cell hyperplasia

	0 mg/kg	1 mg/kg	15 mg/kg	45 mg/kg
Males	2/55 (3.6%)	2/55 (3.6%)	1/55 (1.8%)	1/55 (1.8%)
Females	3/55 (5.5%)	3/55 (5.5%)	0/55 (0.0%)	3/55 (5.5%)

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Neoplastic: The tables below present the neoplastic findings from the study.

		Males				Females			
Rasagiline: mg/kg/day		0	1	15	45	0	1	15	45
Abdominal cavity	# Ex	1	0	2	0	2	3	0	1
Chondrosarcoma		0	0	0	0	1	0	0	0
Adrenal cortex	# Ex	55	37	33	55	55	36	32	55
Adenoma		2	0	0	0	0	0	0	0
Carcinoma		0	0	0	0	1	0	0	0
Spindle cell, carcinoma		0	0	0	0	0	1	0	0
Adrenal medulla	# Ex	55	37	33	55	55	37	32	55
Pheochromocytoma		0	1	0	0	1	0	0	0
Bone, femur	# Ex	55	38	33	55	55	37	31	55
Osteosarcoma		0	1	0	0	0	0	0	0
Bone marrow, femur/sternum,	# Ex	55	38	33	55	55	37	31	54
Leukemia, granulocytic		0	0	0	0	0	1	0	0
Cecum	# Ex	44	26	20	44	47	26	17	33
Leiomyosarcoma		0	0	0	0	1	0	0	0
Myxosarcoma		0	0	0	1	0	0	0	0
Cervix	# Ex					53	40	35	55
Leiomyosarcoma						0	2	0	0
Histiocytic sarcoma						1	1	0	0
Stromal polyp						1	0	0	0
Stromal sarcoma						0	2	0	0
Osteosarcoma						0	0	1	0
Leiomyoma						1	0	0	0
Harderian gland	# Ex	55	54	55	55	55	37	32	55
Adenoma		3	8	11*	9*	2	0	0	3
Carcinoma		0	1	0	0	0	0	0	1
Head, coronal	# Ex	0	1	2	1	0	0	0	0
Osteosarcoma		0	0	1	0	0	0	0	0
Heart	# Ex	55	38	33	55	55	38	33	55
Hemangiosarcoma		0	0	0	1	0	0	0	0
Pericardium, lymphoma, malignant		0	0	0	0	0	0	0	1
Kidney	# Ex	55	55	55	55	55	55	55	55
Tubular cell, adenoma		0	0	1	0	0	0	0	0
Liver	# Ex	55	55	55	55	55	55	55	55
Hepatocellular adenoma		4	5	4	4	1	1	0	2
Hepatocellular carcinoma		2	4	8*	4	0	1	0	0
Histiocytic sarcoma		1	0	0	0	1	1	2	3
Hemangiosarcoma		1	2	0	3	1	0	0	0
Lung	# Ex	55	55	55	55	55	55	55	55
Alveolar bronchiolar adenoma		10	6	17	13	12	8	11	17
Alveolar bronchiolar carcinoma		6	6	9	13*	2	5	8*	5
Lymphoma, malignant		0	0	0	0	0	0	0	1
Leukemia, granulocytic		0	0	0	0	0	1	0	0
Sarcoma, NOS		0	0	0	0	0	2	0	0
Lymph node, Other	# Ex	2	1	3	0	7	7	6	4
Lymphoma, malignant		0	0	0	0	0	1	2	0
Mammary gland	# Ex	18	8	10	8	55	36	26	51
Adenocarcinoma		0	0	0	0	1	2	0	0
Cystadenoma		0	0	0	1	0	0	0	0
Mandibular lymph node	# Ex	52	38	32	51	55	37	32	54
Lymphoma, malignant		0	0	0	0	0	0	0	1
Mesenteric lymph nodes	# Ex	50	39	31	52	54	34	27	48
Lymphoma, malignant		2	1	3	3	4	1	2	3

Text table data extracted from Appendix 11. # Ex = Number examined.
Statistical data extracted from Statistical Report (page 76). * = $p \leq 0.05$.

Figure 95, from page 45 of Report 6751-104

		Males				Females			
Rasagiline: mg/kg/day		0	1	15	45	0	1	15	45
Muscle, other	# Ex	0	0	0	0	1	0	1	0
Hemangiosarcoma		0	0	0	0	1	0	0	0
Ovary	# Ex					54	50	48	55
Cystadenoma						4	0	3	0
Granulosa/thecal cell tumor						0	1	1	1
Pancreas	# Ex	55	38	32	55	55	37	32	55
Islet cell carcinoma		0	0	0	1	0	0	1	0
Pituitary	# Ex	49	38	30	49	54	35	31	53
Adenoma		0	1	0	0	3	0	2	0
Carcinoma		0	0	1	0	0	0	1	0
Skin	# Ex	55	38	33	55	55	37	32	54
Fibrosarcoma		0	0	0	0	1	1	0	0
Skin – Other	# Ex	8	3	2	2	3	2	1	3
Osteosarcoma		0	0	0	1	0	0	0	0
Papilloma		0	0	0	0	0	1	0	0
Spleen	# Ex	55	37	35	55	55	39	38	54
Lymphoma, malignant		0	1	0	1	3	1	1	1
Hemangiosarcoma		0	0	0	0	0	0	1	1
Stomach	# Ex	54	39	33	54	55	37	32	53
Adenocarcinoma		1	0	0	0	0	0	0	0
Nonglandular, squamous polyp		0	1	0	0	0	0	0	0
Glandular, polyp		0	0	0	0	1	0	0	0
Subcutaneous tissue	# Ex	3	0	3	0	3	1	1	5
Squamous cell papilloma		1	0	0	0	0	1	0	1
Hemangiosarcoma		0	0	1	0	0	0	0	0
Fibrosarcoma		0	0	0	0	1	0	0	1
Testis	# Ex	54	40	35	55				
Interstitial cell adenoma		1	2	1	0				
Thymus	# Ex	47	30	27	39	52	38	30	53
Lymphoma, malignant		1	0	0	0	0	4	1	1
Thyroid	# Ex	55	38	33	53	55	37	31	55
Adenoma		0	0	0	1	0	0	0	0
Uterus	# Ex					55	52	47	55
Lymphoma, malignant						0	0	1	0
Hemangiosarcoma						1	0	0	0
Histiocytic sarcoma						1	0	0	0
Stromal polyp						1	4	2	0
Stromal sarcoma						0	0	1	1
Leiomyosarcoma						0	0	1	0
Neurofibroma						1	0	0	0
Vagina	# Ex					54	35	32	55
Leiomyosarcoma						0	0	1	0
Stromal polyp						1	0	0	0
Vertebrae	# Ex	0	0	0	0	0	1	0	0
Osteoma		0	0	0	0	0	1	0	0
Number Animals With Tumors		25	26	36	33	34	29	34	34

Text table data extracted from Appendix 11. # Ex = Number examined.
Statistical data extracted from Statistical Report (page 76).

Figure 96, from page 46 of Report 6751-104

An FDA statistician (Tristan Massie, Ph.D.) has conducted a statistical analysis of the data from this study. At this reviewers request, the statistician has also analyzed the incidence of certain combinations of tumors (lung adenoma/carcinoma, lung alveoloar hyperplasia/adenoma/carcinoma, all lymphomas, all lymphomas/leukemias). These combinations were selected following the guidelines of McConnell et al. (1986).[1] The statistician identified several notable tumor findings (see below).

Table 1 Notable Differences in Tumor Incidences in Mice

	Organ Name	Tumor Name	Control	Low	Mid	High	Control vs. High (Exact Method)	Control vs. High (Asymptotic Method)	Control vs. Mid (Exact Method)	Control vs. Mid (Asymptotic Method)
Females	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	12	8	11	17	0.0119	0.0098	0.0511	0.0333
	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR / BRONCHIOLAR CARCINO	2	6	8 *	5	0.2075	0.2100	0.1645	0.0878
	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	0.3643	0.2085
	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	0.1980	0.1048
Males	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	10	8	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	0.0287	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.

Figure 97, from page 7 of Dr. Massie's Statistical Review of 2/2/04

The FDA statistician concluded that there was adequate survival in both sexes to allow tumor development. Using FDA criteria for significance in trends ($p<0.005$), a significant trend in the incidence of combined bronchioalveolar adenomas and carcinomas was observed in male mice ($p=0.0007$). Trends were also noted for the incidence of adenomas ($p=0.0304$) and carcinomas ($p=0.0065$) alone, but these were not considered significant using FDA criteria. Using pair wise comparison, there an increase

[1] McConnell, EE, HA Solleveld, JA Swenberg and GA Boorman (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Nat. Cancer Inst. 76(2):283-289.

in the incidence of these combined tumors at the high dose (p=0.0045, significant by FDA criteria) in male mice. The increase in mid-dose males for combined adenomas and carcinomas was not considered statistically significant (p=0.04). An increase in the incidence of hepatocellular carcinomas in mid dose males was observed, but in the absence of an effect at the high dose, the biological significance of this observation is unclear. An increased trend in the incidence of harderian gland adenomas in males (p=0.0231) was not considered significant.

In female mice, an increased trend in the incidence of combined bronchioalveolar adenomas and carcinomas was observed (p=0.0071), but was not considered significant by FDA criteria. In addition, an increased trend in bronchioalveolar adenomas was observed, but not considered significant byFDA criteria (p=0.0119). No significant increase was observed in the trend for carcinomas alone (p=0.2075). A non-significant increase in the incidence of carcinomas alone was observed in the mid-dose group (p=0.04)but not in the high dose group (p=0.1645).

The sponsor submitted historical control data for lung neoplasms, which is presented below.

(Total of 226 males and 228 females evaluated in 4 separate studies for each sex)

Lesion	Incidence Range
Males	
Alveolar/bronchiolar Adenoma	6.9% to 28.0%
Alveolar/bronchiolar Adenoma, Multiple	1.7% to 2.9%
Combined Adenoma	8.6% to 28.0%
Alveolar/bronchiolar Carcinoma	12.2% to 23.2%
Alveolar/bronchiolar Carcinoma, Multiple	0% to 4.0%
Combined Carcinoma	12.2% to 26%
Combined Adenoma/Carcinoma	Up to 46%
Females	
Alveolar/bronchiolar Adenoma	12.2% to 16.7%
Alveolar/bronchiolar Adenoma, Multiple	1.4% to 1.7%
Combined Adenoma	12.2% to 18.4%
Alveolar/bronchiolar Carcinoma	6.0% to 18.4%
Alveolar/bronchiolar Carcinoma, Multiple	0% to 1.4%
Combined Carcinoma	6.0% to 18.4%
Combined Adenoma/Carcinoma	Up to 28.6%

1-Data provided by the test facility.

Figure 98, from page 1654 of Report 6751-104

This reviewer requested that the sponsor provide more details on the historical control data including year of study initiation and the incidence of lung tumors in each study. In addition, this reviewer requested that the sponsor submit historical control data on studies initiated after 1998. These data were received on April 28, 2004. The results are summarized below. In male mice, there is a trend towards lower rates of adenomas, carcinomas and combined adenomas/carcinomas. The studies initiated in 1989, 1990 and 1992 have, in general, higher rates lung neoplasms than in studies initiated and 1996 and after. For instance, the range of values for combined adenomas/carcinomas for the 1989-1992 studies was 36.7-46.0%; the range of values for the studied initiated in 1996 or later was 20.7-28.3%. The combined incidence in the present study is 23.6%. The control data in the present study is broadly consistent with the studies initiated after 1996.

Practically speaking, the studies for the later historical control results could not have been initiated after 2001 (to allow time for two years of dosing and histpathological analysis). Thus, all the later historical control data were initiated within about three years of this studies' initiation date. These data would be the most relevant for comparison with the current study.

Male Mouse Historical Control Data for Lung Neoplasm Incidence (percent)

	191DE	227DE	298DE	1019DE	3006DE	3436DE	3493DE	Total	Present
Init date	1989	1990	1992	1996	>1998	>1998	>1998	1989->1998	1998
# mice	50	69	49	58	60	65	60	411	55
Aden	14 (28.0)	13 (18.8)	12 (24.5)	4 (6.9)	11 (18.3)	11 (16.9)	5 (8.3)	70 (17.0)	10 (18.2)
Carc	11 (22.0)	16 (23.2)	6 (12.2)	8 (13.8)	6 (10.0)	4 (6.2)	8 (13.3)	59 (14.4)	6 (10.9)
Comb	23 (46.0)	26 (37.7)	18 (36.7)	12 (20.7)	*17 (28.3)*	*15 (23.1)*	*13 (21.7)*	*124 (30.2)*	13 (23.6)

NOTE: Values in *italics* were obtained by adding the incidence of adenomas and carcinomas together (combined incidence was not broken out in the sponsor submission for these studies). Since it is possible for a single mouse to have both an adenoma and a carcinoma, these values may overestimate the incidence of combined tumors.

Based on the examination of historical control data, it appears that the control incidence in the present study is similar to the incidence in historical control studies. It is therefore concluded that the trend toward increased incidence of lung neoplasms in this study is not the result of random variation but is a drug related finding.

In contrast, the historical control data for the female mice are broadly consistent over time. The incidence of carcinomas in the 1989 study is twice as high as the incidence in any other study. There does not appear to be any significant drift in the incidence of adenomas or combined adenoma/carcinoma with time. The control data for the present study had a slightly higher incidence of adenomas with a lower incidence of carcinomas. The combined data were consistent with previous studies.

Female Mouse Historical Control Data for Lung Neoplasm Incidence (percent)

	191DE	227DE	298DE	1002DE	3007DE	3437DE	3494DE	Total	Present
Init date	1989	1990	1992	1996	>1998	>1998	>1998	1989->1998	1998
# mice	49	69	50	60	60	65	60	413	55
Aden	6 (12.2)	10 (14.5)	7 (14.0)	10 (16.7)	10 (16.7)	16 (24.6)	6 (10.0)	65 (15.7)	12 (21.8)
Carc	9 (18.4)	6 (8.7)	3 (6.0)	5 (8.3)	4 (6.7)	5 (7.7)	4 (6.7)	36 (8.7)	2 (3.6)
Comb	14 (28.6)	17 (24.6)	10 (20.0)	16 (26.7)	*14 (23.3)*	*21 (32.3)*	*10 (16.7)*	*103 (24.9)*	13 (23.6)

NOTE: Values in *italics* were obtained by adding the incidence of adenomas and carcinomas together (combined incidence was not broken out in the sponsor submission for these studies). Since it is possible for a single mouse to have both an adenoma and a carcinoma, these values may overestimate the incidence of combined tumors.

Toxicokinetics:
Males were exposed to higher levels of rasagiline and AI at 45 mg/kg compared to females on Day 30 of the study.

Test Table 1
Rasagiline (PAI)

Group (Rasagiline mg/kg/day)		AUC$_{0-t}$ (ng·h/mL)		$t_{1/2}$ (h)		C_{max} (ng/mL)		T_{max} (h)	
		Male	Female	Male	Female	Male	Female	Male	Female
2	(1)	65	53	0.75	0.53	83.2	64.8	0.25	0.25
3	(15)	2349	1933	1.26	1.54	2071.0	1260.0	0.25	0.25
4	(45)	15873	5813	3.35	1.69	4346.7	2741.0	0.25	0.25

Test Table 2
Aminoindan (AI)

Group (Rasagiline mg/kg/day)		AUC$_{0-t}$ (ng·h/mL)		$t_{1/2}$ (h)		C_{max} (ng/mL)		T_{max} (h)	
		Male	Female	Male	Female	Male	Female	Male	Female
2	(1)	202	201	1.90	1.46	147.3	94.3	0.5	0.5
3	(15)	5341	4886	3.36	2.88	1520.0	1243.3	0.5	1.0
4	(45)	25820	10971	5.31	2.87	2836.7	1960.0	2.0	0.5

Figure 93, from page 15 of Report 6751-104

Conclusions:
It is concluded that rasagiline increased the incidence of combined lung adenomas/carcinomas in male mice.
A non-significant increase was also observed in the incidence of combined lung adenomas/carcinomas in female mice.
An MTD was not observed in female mice.

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3.4.5.1 RASAGILINE MESYLATE (TVP-1012) CARCINOGENICITY STUDY BY ORAL GAVAGE ADMINISTRATION TO - .:CD®(SD)IGS BR RATS FOR 104 WEEKS

Key study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:
1. This study only examined the incidence of tumors in high dose and control rats.
2. The high dose in both males and females exceeded the Maximum Tolerated Dose (MTD) as evidenced by an excessive loss of weight (greater than 20%).

Evaluation of tumor findings:
1. No significant increase in tumor findings were observed.
2. Since the high dose exceeded the MTD, the low and mid-dose groups should be evaluated for neoplasms to make this a valid study.

Study no.: 6751-109
Location: \tox\6751-109.pdf
Conducting laboratory and location: '
Date of study initiation: January 19, 1998
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: 255495223, 255400199
CAC concurrence: The Exec CAC (May 27, 1997) recommended doses of 0.3, 1 and 3.0 mg/kg in males and 0.5, 2, 5 and 17 mg/kg in females. It was also recommended that the rats be housed individually. There was no discussion of histopathology only being conducted in control and high dose animals.

Methods

Doses: 0, 0, 0.3, 1.0, 3.0, 17.0 (females only)
Basis of dose selection (MTD, MFD, AUC etc.):
Species/strain: Rat, CD®(SD)IGS BR
Number/sex/group (main study): 65/sex/dose
Route, formulation, volume: oral gavage in distilled water, 10 mg/kg/day
Frequency of dosing: 1/day
Satellite groups used for toxicokinetics or special groups: 15/sex/dose
Age: 7 weeks
Animal housing: Individually housed in hanging wire cages
Restriction paradigm for dietary restriction studies: NA
Drug stability/homogeneity: Drug stable
Dual controls employed: Yes
Interim sacrifices: None
Deviations from original study protocol: no significant deviations

Observation times
Mortality: 2X/day
Clinical signs: 1X/day
Body weights: 1X/week (weeks 1-14), 1X/2 weeks (weeks 15-105)
Food consumption: 1X/week (weeks 1-13), 1X/2 weeks (weeks 14-104)
Histopathology: Peer review: yes (X), no ( ); Complete histopathological examination; Control and high dose only; gross lesions only at low and mid doses;
Toxicokinetics: Day 30, Week 52/53, 78; pre, 0.25, 0.5, 1, 2, 4 hours post dose; 4/rats/sex/dose
Other Studies: Prolactin and luteinizing hormone in control 1 and high dose rats during weeks 14 and 29

Results

Mortality: No statistically significant effects on mortality were observed.

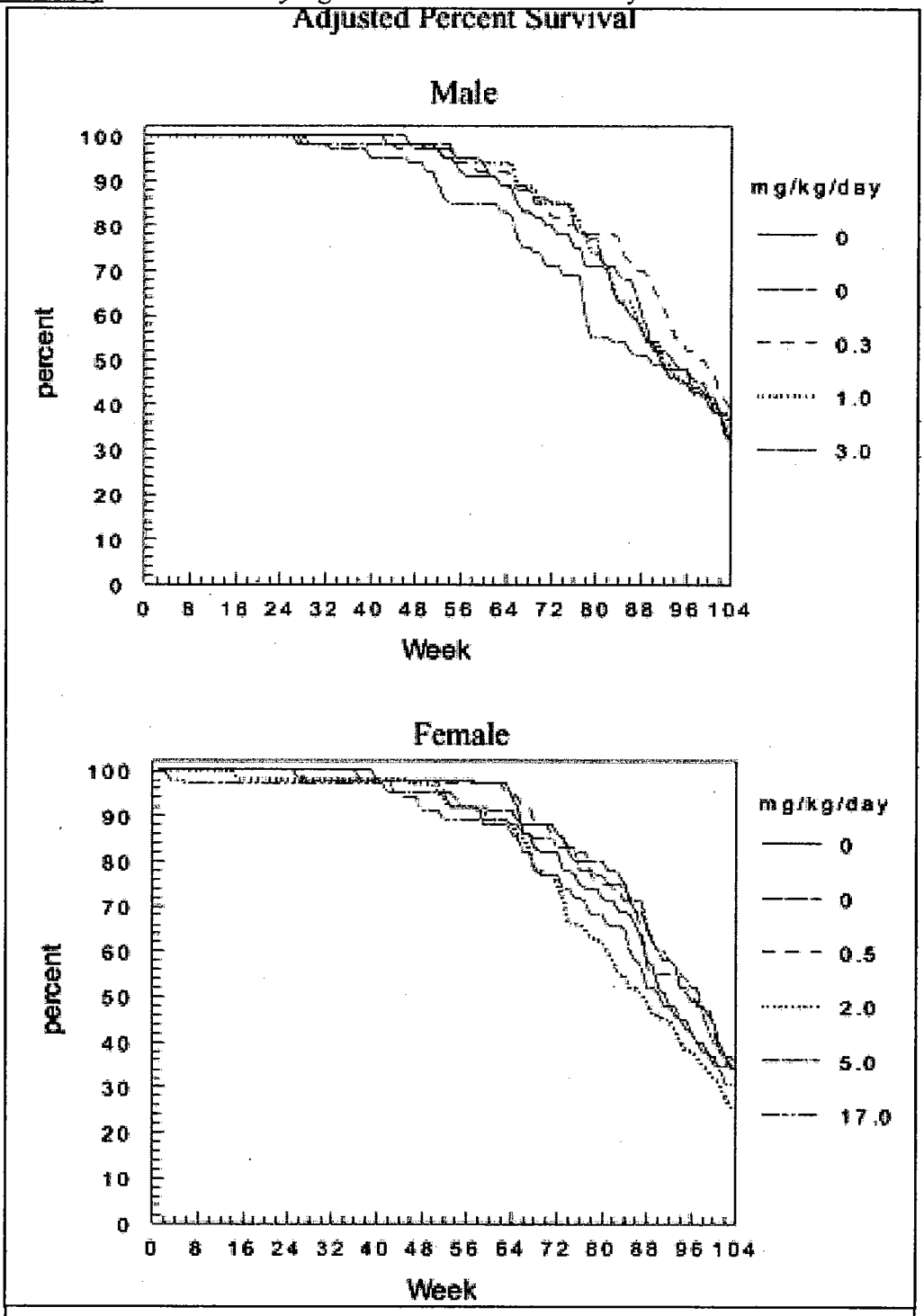

Figure 99, from page 31 of Report 6751-109

Clinical signs:

Summary of Drug-Related Clinical Observations[a]

	Male					Females					
mg/kg/day	0	0	0.3	1	3	0	0	0.5	2	5	17
Swollen Paws	11	12	17	27	37	4	2	5	20	23	15
Paw Sore/Scab	17	21	26	36	44	9	13	16	37	42	35
Aggressive Behavior	0	0	0	0	6	0	0	0	1	1	2
Hyperactivity	0	0	0	0	15	0	0	0	7	19	35
Alopecia	14	14	19	14	27	18	17	15	32	30	27
Yellow Hair Coat	10	7	11	12	6	3	7	4	7	17	30
Malocclusion	6	3	5	8	15	0	4	5	6	9	9
Red nasal discharge	1	4	2	3	4	4	6	5	2	5	12
Swollen Axillary region	2	1	3	1	2	14	11	14	12	10	4
Swollen Ventral region	14	14	14	10	3	23	20	28	21	14	5
Mass	18	10	24	13	5	39	35	36	30	28	20

a Number of animals effected.

Figure 100, from page 33 of Report 6751-109

Several clinical signs were associated with rasagiline treatment. None of these signs would be considered dose limiting.

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Body weights:

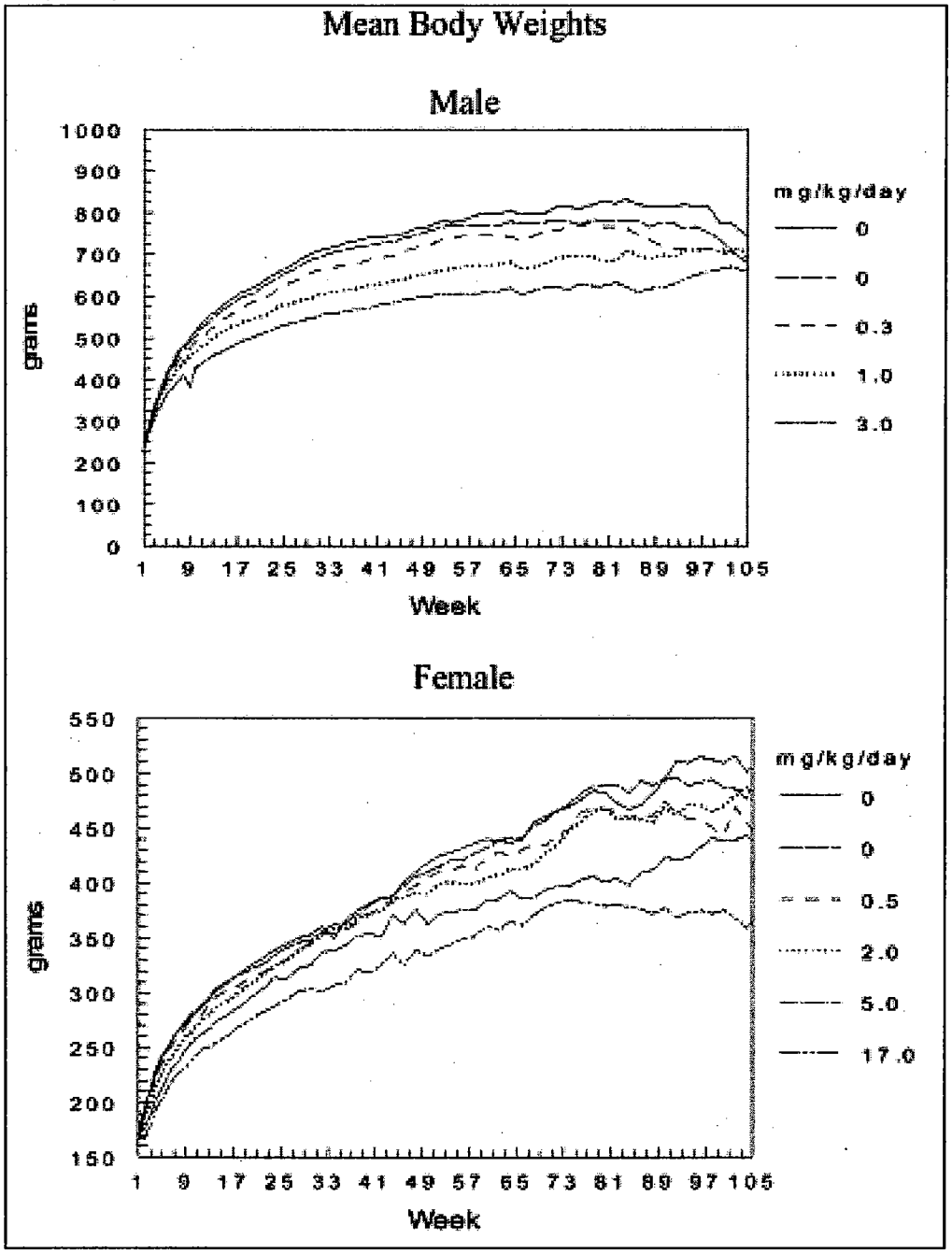

Figure 101, from page 34 of Report 6751-109

Summary of Mean Body Weights and Weights Gains (g)

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 body weight gains in grams (% difference compared to Group 1 control)					
Week 1-13	335	327 (-2%)	305 (-9%)*#	283 (-16%)*#	231 (-31%)*#
Week 1-27	453	441 (-3%)	408 (-10%) *#	362 (-20%) *#	311 (-31%) *#
Week 1-51	544	532 (-2%)	501 (-8%) *#	434 (-20%) *#	374 (-31%) *#
Week 1-77	586	552 (-6%)	542 (-8%)	469 (-20%) *#	395 (-33%) *#
Week 1-104	512	440 (-14%)	466 (-9%)	484 (-5%)	436 (-15%)

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%) *#	275 (-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 body weight gains in grams (% difference compared to Group 1 control)						
Week 1-13	127	131 (3%)	127 (0%)	115 (-9%) *#	104 (-18%) *#	86 (-32%) *#
Week 1-27	177	175 (-1%)	170 (-4%)	167 (-6%)	153 (-14%) *#	132 (-25%) *#
Week 1-51	251	244 (-3%)	242 (-4%)	229 (-9%)	205 (-19%) *#	172 (-31%) *#
Week 1-77	311	318 (2%)	301 (-3%)	296 (-5%)	238 (-23%) *#	214 (-31%) *#
Week 1-104	334	306 (-8%)	279 (-16%)	315 (-6%)	271 (-19%)	199 (-40%) *#

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

Figure 102, from page 35 of Report 6751-109

Excessive weight loss (>10%) was observed at 1 and 3 mg/kg in males and 5 and 17 mg/kg in females.

Food consumption:

Summary of Mean Total Food Consumption Values (g)

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 total food consumption in grams (% difference compared to Group 1 control)					
Week 1-13	2825	2769 (-2%)	2719 (-4%) *	2588 (-8%) *#	2396 (-15%) *#
Week 1-27	4310	4222 (-2%)	4086 (-5%) *#	3826 (-11%) *#	3594 (-17%) *#
Week 1-51	6904	6796 (-2%)	6582 (-5%) *	6057 (-12%) *#	5725 (-17%) *#
Week 1-77	9811	9660 (-2%)	9365 (-5%) *	8714 (-11%) *#	8217 (-16%) *#
Week 1-104	12665	11985 (-5%)	12238 (-3%)	11441 (-10%)*	11565 (-9%) *

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 total food consumption in grams (% difference compared to Group 1 control)						
Week 1-13	1904	1940 (2%)	1915 (1%)	1846 (-3%) *#	1743 (-8%) *#	1693 (-11%) *#
Week 1-27	2855	2891 (1%)	2894 (1%)	2808 (-2%)	2689 (-6%) *#	2653 (-7%) *#
Week 1-51	4676	4707 (1%)	4745 (1%)	4659 (0%)	4540 (-3%) #	4450 (-5%) *#
Week 1-77	6714	6901 (3%)	6806 (1%)	6655 (-1%)	6475 (-4%) #	6418 (-4%) *#
Week 1-104	8966	8906 (-1%)	9195 (3%)	8494 (-5%)	8473 (-5%)	8400 (-6%) *

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

Figure 103, from page 37 of Report 6751-109

Hematology/Prolactin Levels:
No effects were observed on hematological parameters.
Female 17 mg/kg prolactin level was decreased at week 29 (146 vs 350 in controls) but not at week 14 (129 versus 127 in controls). No changes were observed in males. No significant changes were observed in luteinizing hormone in either sex at week 14 (only time examined).

Gross pathology:
Males

	0 mg/kg	0 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg
Swollen Foot	7/65	11/65	14/65	26/65	36/65
Foot Sores	12/65	19/65	24/65	32/65	38/65

Females

	0 mg/kg	0 mg/kg	0.5 mg/kg	2 mg/kg	5 mg/kg	17 mg/kg
Swollen Foot	3/65	1/65	6/65	16/65	24/65	18/65
Foot Sores	9/65	9/65	9/65	29/56	35/65	31/65

Histopathology:

Non-neoplastic:

The primary non-neoplastic findings consisted of chronic skin inflammation associated with foot sores in rats treated with 0.3 mg/kg and above in males and 2.0 mg/kg and above in females.

In addition, urogenital tract inflammation characterized by inflammation and hemorrhage of the urinary bladder with dilatation of the kidney and tules and tubular degernation was more common in rats treated with 3 mg/kg. This is a constellation of signs, which were not broken out individually, however the group incidence of these signs were higher than in other dose groups or in terminal sacrifice 3 mg/kg male rats.

Comparison of Kidney and Urinary Bladder in Early Decedents and in High Dose Terminally sacrificed Male Rats.

	0 mg/kg	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg Early	3.0 mg/kg Terminal
Kidney, tubule degeneration	2/45	1/45	0/41	3/43	11/41	1/24
Kidney, tubule dilation	4/45	2/45	3/41	3/43	13/41	0/24
Urinary bladder, acute inflammation	8/45	4/45	5/41	7/43	14/41	0/24
Urinary bladder, hemorrhage	4/45	2/45	2/41	5/43	16/41	0/24

Neoplastic:

Text Table 7. Incidences of Animals with Primary Neoplasms in All Animals

Tissue/Neoplasm	Males					Females					
Treatment Group	1	2	3	4	5	1	2	3	4	5	6
Rasagiline mesylate (TVP-1012) Base (mg/kg/day)	0.0	0.0	0.3	1.0	3.0	0.0	0.0	0.5	2.0	5.0	17.0
Brain (number examined)	(65)	(65)	(44)	(46)	(65)	(65)	(65)	(55)	(53)	(51)	(65)
M-Astrocytoma	2	–	–	–	1	1	–	–	2	1	1
M-Oligodendroglioma	–	–	–	1	–	–	–	–	–	–	–
B-Granular cell tumor	–	1	–	–	–	–	–	–	–	–	–
Thyroid	(65)	(65)	(42)	(43)	(65)	(65)	(65)	(42)	(49)	(46)	(63)
M-C cell carcinoma	–	1	1	–	1	–	–	–	–	1	1
B-C cell adenoma	4	3	3	3	6	5	6	3	3	1	2
M-Follicular cell carcinoma	1	–	1	–	–	1	3	–	1	1	1
B-Follicular cell adenoma	–	4	2	5	1	–	2	–	–	1	–
Parathyroid	(58)	(62)	(37)	(39)	(52)	(56)	(47)	(34)	(43)	(37)	(57)
B-Adenoma	–	–	–	1	–	–	–	–	–	–	–
Pancreas	(65)	(64)	(39)	(43)	(65)	(65)	(65)	(42)	(48)	(44)	(64)
M-Islet cell carcinoma	–	1	–	–	–	1	–	–	–	–	1
B-Islet cell adenoma	5	3	2	3	2	2	–	–	–	–	–
M-Acinar cell carcinoma	1	–	–	–	–	–	–	–	–	–	–
B-Acinar cell adenoma	–	–	–	–	–	–	1	–	–	–	–
M-Sarcoma, NOS	–	1	–	–	–	–	–	–	–	–	–
Spinal Cord, Lumbar	(65)	(65)	(40)	(43)	(65)	(64)	(65)	(42)	(49)	(45)	(65)
M-Astrocytoma	–	–	–	1	–	–	–	–	–	–	–
Adrenal Cortex	(65)	(65)	(43)	(44)	(65)	(65)	(65)	(52)	(58)	(53)	(65)
M-carcinoma	1	1	–	–	1	2	–	–	–	1	–
B-adenoma	1	1	–	–	2	1	1	2	1	–	–
Adrenal Medulla	(65)	(64)	(44)	(42)	(66)	(65)	(64)	(48)	(58)	(50)	(64)
M-Pheochromocytoma	5	4	2	–	2	–	–	–	–	–	–
B-Pheochromocytoma	10	8	4	2	3	2	2	1	1	1	1
Pituitary	(65)	(64)	(48)	(50)	(65)	(64)	(65)	(59)	(59)	(61)	(65)
B-Adenoma	42	51	39	30	33	57	57	56	50	56	51
M-Carcinoma	–	–	–	–	–	–	–	–	1	–	–
M-Astrocytoma (pars nervosa)	1	1	–	–	1	–	–	–	–	–	–
Thymus	(56)	(56)	(38)	(40)	(61)	(59)	(61)	(41)	(47)	(43)	(62)
M-Thymoma	–	–	–	–	–	–	–	1	1	–	–
Heart	(65)	(65)	(41)	(43)	(65)	(65)	(65)	(42)	(49)	(45)	(65)
M-Neurofibrosarcoma	–	–	–	1	1	–	–	–	–	–	–
M-Atrioventricular mesothelioma	–	1	–	–	–	–	–	–	–	–	–
Jejunum	(55)	(50)	(31)	(34)	(47)	(51)	(54)	(32)	(35)	(33)	(54)
M-Carcinoma	1	–	–	–	–	–	–	–	–	–	–
Duodenum	(55)	(57)	(39)	(35)	(58)	(61)	(65)	(37)	(39)	(37)	(63)
M-Carcinoma	–	1	–	–	–	–	–	–	–	–	–

Figure 104, from page 73 of Report 6751-109

Liver	(65)	(65)	(46)	(48)	(65)	(65)	(65)	(45)	(52)	(48)	(65)
M-Hepatocellular carcinoma	–	2	3	2	–	–	1	–	–	–	1
B-Hepatocellular adenoma	1	–	–	–	–	1	–	–	–	–	–
B-Cholangioma	–	–	–	1	–	–	–	1	–	–	–
Spleen	(65)	(66)	(43)	(43)	(61)	(65)	(65)	(43)	(48)	(48)	(65)
M-Hemangiosarcoma	1	–	–	–	–	–	–	–	–	–	–
Mammary, Caudal, Female	na	na	na	na	na	(64)	(64)	(52)	(55)	(50)	(63)
M-Adenocarcinoma						5	4	5	6	1	–
B-Fibroadenoma						15	22	17	11	13	5
B-Adenoma						1	2	1	2	3	1
B-Fibroma						–	–	–	1	–	–
M-Neurofibrosarcoma						–	–	–	2	–	–
M-Sarcoma, NOS						–	–	–	1	–	–
Mammary, Cranial, Female	na	na	na	na	na	(61)	(59)	(50)	(49)	(50)	(57)
M-Adenocarcinoma						–	7	4	–	–	1
B-Fibroadenoma						20	12	12	9	12	12
B-Adenoma						–	–	–	1	–	–
M-Fibrosarcoma						–	1	–	–	–	–
Mammary, Cranial & Caudal Combined, Females	na	na	na	na	na	(64)	(64)	(52)	(55)	(50)	(63)
M-Adenocarcinoma						5	10	9	6	1	1
B-Fibroadenoma						30	27	25	18	20	15
B-Adenoma						1	2	1	3	3	1
M-Fibrosarcoma						–	1	–	–	–	–
M-Sarcoma, NOS						–	–	–	1	–	–
B-Fibroma						–	–	–	1	–	–
M-Neurofibrosarcoma						–	–	–	2	–	–
Mammary, Male	(5)	(4)	(6)	(2)	(2)	na	na	na	na	na	na
B-Fibroadenoma	–	1	–	–	–						
B-Fibroma	2	1	3	1	–						
B-Lipoma	–	–	1	–	–						
Lung	(65)	(66)	(42)	(43)	(65)	(65)	(65)	(42)	(49)	(46)	(65)
M-Leiomyosarcoma	–	–	–	–	–	–	–	–	–	–	1
Mesenteric Lymph Node	(65)	(65)	(41)	(43)	(62)	(63)	(65)	(42)	(50)	(44)	(64)
M-Hemangiosarcoma	–	1	–	1	–	–	–	–	–	–	–
B-Hemangioma	–	–	–	–	1	–	–	–	–	–	–
Kidney	(65)	(65)	(47)	(45)	(65)	(65)	(65)	(44)	(50)	(47)	(65)
M-Tubular cell carcinoma	–	1	–	–	–	–	–	–	–	–	–
M-Liposarcoma	1	–	–	–	–	–	2	–	–	–	–
B-Lipoma	–	–	1	–	–	–	1	–	1	–	–
Testis	(65)	(65)	(42)	(43)	(64)	na	na	na	na	na	na
B-Interstitial cell tumor	1	3	–	–	3						
B-Seminoma	1	–	–	–	–						

Figure 105, from page 74 of Report 6751-109

Prostate	(64)	(65)	(43)	(44)	(65)	na	na	na	na	na	na
M-Carcinoma	–	1	–	–	–						
Ovary	na	na	na	na	na	(63)	(65)	(46)	(53)	(47)	(65)
M-Sertoli cell tumor						–	1	–	–	–	–
B-Granulosa/theca cell tumor						–	–	–	–	1	2
B-Interstitial gland adenoma						–	1	–	–	–	–
Oviduct	na	na	na	na	na	(1)	(0)	(0)	(0)	(0)	(0)
B-Adenoma						1	–	–	–	–	–
Uterus	na	na	na	na	na	(64)	(65)	(50)	(53)	(50)	(65)
B-Leiomyoma						–	1	–	1	–	1
B-Endometrial stromal polyp						6	4	–	2	3	5
Uterus, Cervix	na	na	na	na	na	(64)	(65)	(43)	(49)	(46)	(65)
M-Neurofibrosarcoma						1	–	–	–	–	–
B-Leiomyoma						–	–	–	–	–	1
B-Fibroma						1	–	–	–	–	–
Vagina	na	na	na	na	na	(63)	(65)	(42)	(49)	(45)	(65)
M-Neurofibrosarcoma						1	1	–	–	–	–
Clitoral Gland	na	na	na	na	na	(1)	(0)	(0)	(0)	(0)	(1)
B-Squamous cell papilloma						–	–	–	–	–	1
Hematopoietic Neoplasia	(65)	(65)	(44)	(43)	(65)	(65)	(65)	(43)	(49)	(45)	(65)
M-Histiocytic sarcoma	3	2	4	2	–	–	1	1	1	1	2
M-Lymphoma	–	–	–	–	–	–	–	1	1	1	1
M-LGL leukemia	–	1	–	2	1	–	–	–	–	–	–
Skin, Other	(28)	(29)	(37)	(42)	(48)	(17)	(16)	(19)	(39)	(43)	(33)
M-Squamous cell carcinoma	2	1	–	1	1	–	–	–	2	–	–
M-Neurofibrosarcoma	1	–	1	1	1	2	–	2	1	–	–
M-Fibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Melanoma	–	–	–	–	1	–	–	–	–	–	–
B-Keratoacanthoma	2	3	3	1	3	–	–	–	1	–	–
B-Squamous cell papilloma	5	3	1	1	1	–	1	–	–	1	–
B-Sebaceous adenoma	–	–	–	–	2	–	–	–	–	–	–
B-Basal cell adenoma	–	–	–	–	–	–	–	–	1	–	–
B-Fibroma	–	–	3	1	1	–	–	–	–	–	–
B-Lipoma	1	–	–	–	–	–	–	–	–	–	–
Subcutaneous Tissue	(3)	(2)	(4)	(3)	(4)	(1)	(2)	(2)	(2)	(0)	(1)
M-Neurofibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Sarcoma, NOS	–	–	1	–	–	–	2	–	–	–	–
M-Fibrosarcoma	–	–	–	–	–	–	–	–	1	–	–
M-Malig. fibrous histiocytoma	–	–	–	–	–	1	–	–	–	–	–
M-Hemangiosarcoma	–	–	–	–	–	–	–	1	–	–	–
B-Fibroma	1	1	–	1	1	–	–	–	1	–	1
B-Lipoma	1	–	–	–	1	–	–	–	–	–	–
Cavity, Abdominal	(4)	(1)	(2)	(1)	(0)	(0)	(0)	(1)	(1)	(1)	(2)
N-Neurofibrosarcoma	–	–	–	–	–	–	–	–	–	–	1

Figure 106, from page 75 of Report 6751-109

Head, Cranial	(1)	(3)	(1)	(0)	(2)	(1)	(1)	(0)	(1)	(0)	(0)
M-Neurofibrosarcoma	–	–	1	–	–	–	–	–	–	–	–
M-Carcinoma, squamous cell	–	1	–	–	–	–	–	–	–	–	–
Oral Cavity	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
B-Squamous cell papilloma	–	–	–	1	–	–	–	–	–	–	–

(##) Numbers in parentheses represent number of animals for which that tissue was examined. For combined mammary glands (female), the number examined listed was the higher of the two individual glands.
M Malignant; Malig. Malignant
B Benign
- Incidence of zero
NOS Not otherwise specified
na non-applicable, gender specific tissue
LGL Large granular lymphocyte

Figure 107, from page 76 of Report 6751-109

FDA statistician (Tristan Massie, Ph.D.) has conducted a statistical analysis of the data from this study. At this reviewers request, the statistician has also analyzed the incidence of certain combinations of tumors (all lymphomas, all lymphomas/leukemias). These combinations were selected following the guidelines of McConnell et al. (1986).[2] The statistician concluded that there were no noteworthy increases or trends in tumor incidence.

Toxicokinetics:

Toxicokinetic Summary of TVP-1012

	Male			Female			
mg/kg/day	0.3	1.0	3.0	0.5	2.0	5.0	17.0
C_{max} (ng/ml)							
Day 30	19.88	77.50	345.25	50.89	250.00	687.00	3017.50
Week 26	30.93	122.25	474.50	37.10	435.75	688.75	2255.00
Week 52	54.35	150.45	717.25	67.75	458.75	914.75	2555.50
T_{max} (hr)							
Day 30	0.25	0.50	0.25	0.25	0.25	0.25	0.25
Week 26	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Week 52	0.25	0.50	0.25	0.25	0.25	0.25	0.25
AUC_{0-4} ng*hr/ml							
Day 30	25.65	91.48	446.79	48.14	234.61	761.80	3509.13
Week 26	43.75	172.32	642.40	72.89	355.75	964.79	3044.00
Week 52	58.51	233.63	829.45	72.45	394.63	1149.59	4368.05
$t_{1/2}$ (hr)							
Day 30	0.77	0.79	0.88	0.85	0.72	1.03	1.18
Week 26	1.22	1.18	1.20	0.89	1.09	1.29	1.75
Week 52	1.09	1.05	1.12	1.06	0.96	1.14	1.56

C_{max} = Maximum or peak concentration.
T_{max} = Time to achieve maximum concentration.
AUC_{0-4} = $\int$ [C(t)] dt = area under the concentration curve [C(t)] from 0 to 4 hours.
$t_{1/2}$ = Half-life of first order (terminal) elimination.

Figure 108, from page 45 of Report 6751-109

[2] McConnell, EE, HA Solleveld, JA Swenberg and GA Boorman (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Nat. Cancer Inst. 76(2):283-289.

Toxicokinetic Summary of Aminoindan

	Male			Female			
mg/kg/day	0.3	1.0	3.0	0.5	2.0	5.0	17.0
C_{max} (ng/ml)							
Day 30	14.36	43.92	104.68	38.70	133.50	263.50	811.25
Week 26	16.10	44.98	113.38	39.03	130.30	258.50	584.00
Week 52	14.22	46.52	127.00	46.52	148.00	318.25	910.25
T_{max} (hr)							
Day 30	0.50	0.50	0.50	1.00	0.50	0.50	1.00
Week 26	0.50	0.50	0.50	0.25	0.50	1.00	2.00
Week 52	1.00	1.00	1.00	0.50	0.50	1.00	2.00
AUC_{0-4} ng-hr/ml							
Day 30	31.75	111.37	294.48	88.66	383.69	849.32	2626.45
Week 26	36.97	112.80	327.50	113.02	364.56	774.31	1845.68
Week 52	44.01	130.27	412.18	133.77	429.40	1011.89	3026.64
$t_{1/2}$ (hr)							
Day 30	2.21	2.01	2.58	1.80	2.55	3.41	3.86
Week 26	2.77	2.65	3.39	2.68	3.89	3.27	4.45
Week 52	3.05	3.49	5.01	2.82	2.94	2.83	5.74

C_{max} = Maximum or peak concentration.
T_{max} = Time to achieve maximum concentration.
AUC_{0-4} = $\int_0^4 C(t)\,dt$ = area under the concentration curve [C(t)] from 0 to 4 hours.
$t_{1/2}$ = Half-life of first order (terminal) elimination.

Figure 109, from page 46 of Report 6751-109

CONCLUSIONS

It is concluded that no significant increase in tumor incidence was observed in male or female rats. However, complete histopathological examination was conducted only on the control and high dose animals. Since the high dose exceeded the MTD, the lower dose groups should have been examined. The sponsor will need to conduct this analysis to make this a valid study.

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3.4.6. Reproductive and developmental toxicology

3.4.6.1 TOXICITY STUDY ON MALE FERTILITY WITH RASAGILINE MESYLATE (TVP-1012) IN THE RAT

Key study findings:
1. Rats did not tolerate 5 mg/kg; high dose was lowered to 3 mg/kg.
2. No significant effects were noted on sperm or reproductive parameters.
3. Decreased prolactin levels were observed.

Study no.: — Project 660036
Location:
Conducting laboratory and location: —
—
Date of study initiation: August 25, 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 225 495 223

Methods

Doses: 0, 0.5, 2.0, 5.0 mg/kg/day; dose was lowered to 0.3, 1.0 and 3.0 mg/kg on Day 19 due to excessive toxicity at the high dose.

Species/strain: Rat, OFA Sprague-Dawley

Number/sex/group: 22 males/group

Route, formulation, volume, and infusion rate:

Satellite groups used for toxicokinetics:

Study design: Male rats treated for 28 days prior to mating with untreated females; females sacrificed 14 days post coitus.

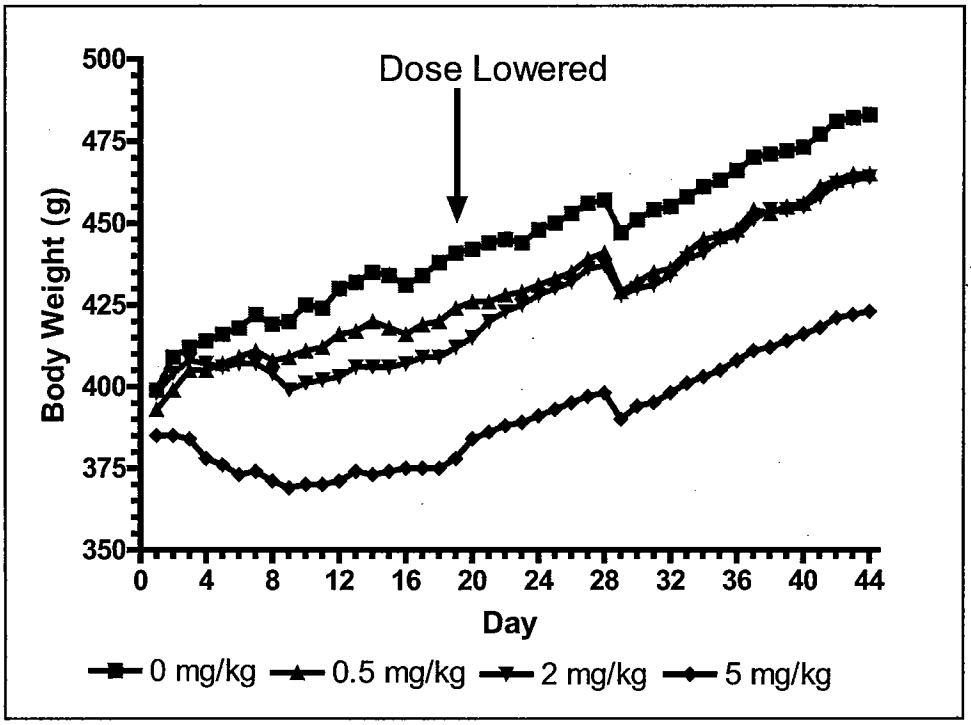
Parameters and endpoints evaluated: male fertility, sperm analysis, serum prolactin.

Results

Mortality:
One low dose (0.5 mg/kg) male (#41) was found dead on Day 42. Death was ascribed to urinary tract infection; rat piloerection, sedation, abdominal position and dyspnea on Days 40 and 41.

Clinical signs:
All high dose rats had increased aggression and piloerection on Day 4 of dosing. Slightly increased aggression was noted in all high dose rats on days 20 and 27.
No other clinical signs were reported in any group.

Body weight: Decreased body weight, particularly at 5 mg/kg.



Day 44 Body weights (SD)

	0 mg/kg	0.5 mg/kg	2.0 mg/kg	5.0 mg/kg
Body Weight in g	483 (35.4)	465 (25.9)	464 (26.7)	**423 (29.6)**
% of Control	100%	96%	96%	88%

Value in **Bold** significantly different from control ($p<0.01$).

Food consumption:
Decreased relative food consumption was observed at 2 and 5 mg/kg, (-10 and -18%, respectively), but after the dose was reduced on Day 19, relative food consumption was similar among the groups (within 4% of control).

Toxicokinetics:
Not done

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Necropsy:
No particular findings; histopathology was not performed.

Group	Number of males examined	Number of males without findings	Number of males with findings						
			A	B	C	D	E	F	G
1	22	21		1					
2	22	19	1			1	1		
3	22	19	2		1		1	1	
4	22	19	2						1

A = Testes reduced in size
B = Testes contains watery fluid
C = Deferent duct reduced in size
D = (Spontaneous death of animal no 41, group 2), multiple findings in kidneys, urinary bladder, prostate, seminal vesicles, adrenal gland, thymus and body cavities (see p. 94)
E = Seminal vesicles reddish discoloration
F = Epididymides organ missing
G = Cryptorchism

Figure 110, from page 24 of — Project 660036

Rat 41 had enlarged hemorrhagic kidneys while the thoracic and abdominal cavities contained watery clear fluid.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
Some increase in time to mating was observed at the mid-dose (mating within 4-5 days is considered normal (The Laboratory Rat, GJ Krinke (ed), page 217).

NUMBER OF FEMALES MATED DURING THE FIRST PAIRING PERIOD

Day of the pairing period	GROUP 1 0 MG/KG	GROUP 2 0.5 / 0.3 MG/KG	GROUP 3 2.0 / 1.0 MG/KG	GROUP 4 5.0 / 3.0 MG/KG
1	5	8	4	6
2	6	5	4	5
3	5	2	6	3
4	3	5	2	3
5	2	2	1	1
9	-	-	1	-
10	1	-	-	-
12	-	-	0	2
Median precoital time	3	2	3	3
Mean precoital time	3.9	3.5	4.5	3.5
N	22	22	22	22

Figure 111, from page 59 of — Project 660036

No other effects on mating parameters (pregnancy rate, time to mating).
No effects on sperm motility, concentration or morphology were observed.

Decreased prolactin levels (ng/ml) were observed

	0 mg/kg	0.5 mg/kg	2.0 mg/kg	5.0 mg/kg
Mean	50.74	**33.90**	**17.99**	**12.30**
SD	31.93	26.90	7.97	4.98

Values in **Bold** significantly different from control ($p<0.05$).

3.4.6.2 RASAGILINE MESYLATE (TVP-1012) COMBINED STUDY FOR EFFECTS ON FEMALE FERTILITY AND EMBRYO-FETAL DEVELOPMENT AFTER ORAL ADMINISTRATION (GAVAGE) IN THE RAT

Key study findings:
1. No adverse effect on female fertility or embryo-fetal development was observed in female rats administered up to 3 mg/kg.
2. The 3 mg/kg dose caused decreased weight in rats during the premating period.
3. AUC(0-8) and Cmax values were increased two to four fold in pregnant rats compared to non-pregnant rats.

Study no.: — Project 806916
Location: /tox/ Project 806916.pdf
Conducting laboratory and location: —
Date of study initiation: May 21, 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 255400100

Methods

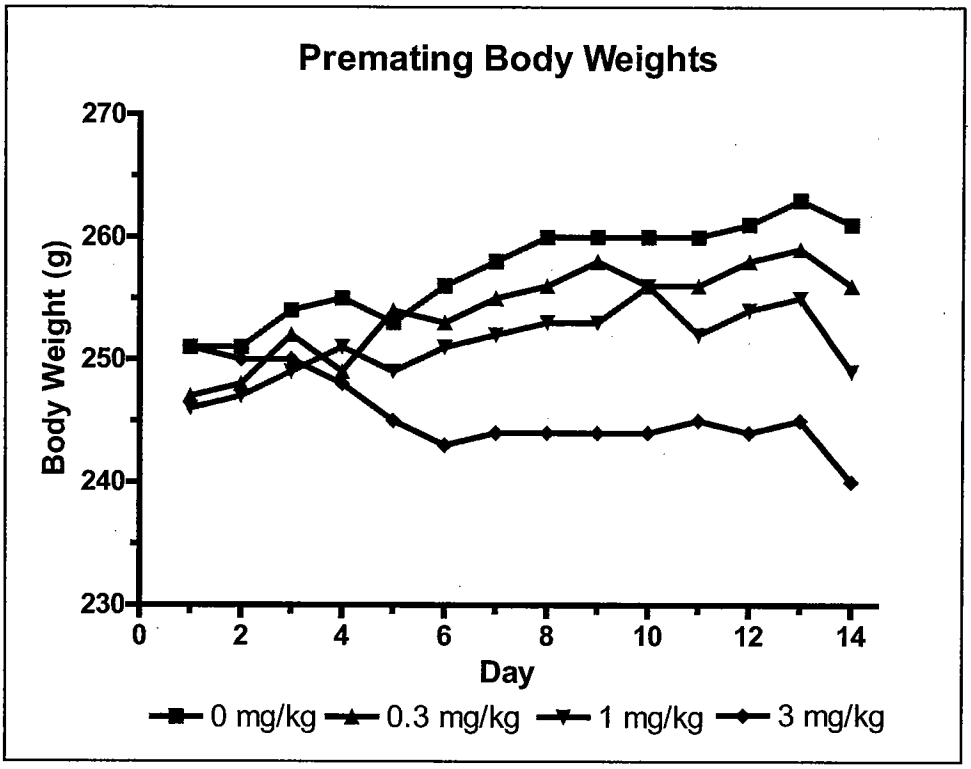
Doses: 0, 0.3, 1.0, 3.0 mg/kg
Species/strain: Rat Icolbm: OFA Sprague Dawley
Number/sex/group: 22 females/group
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: 9 females/dose group
Study design: females were treated from 14 days premating through gestation day 17; females were mated with untreated male; females were sacrificed on day 21 of gestation.
Parameters and endpoints evaluated: female fertility, embryo-fetal development

Results

Mortality:
There was no early mortality.

Clinical signs:
No clinical signs were observed in treated rats.

Body weight:
Decreased body weight was observed at 3 mg/kg prior to mating. Body weight gain during gestation were similar among the groups



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DIFFERENCES IN MEAN BODY WEIGHT GAIN (G) OF DAMS - GESTATION PERIOD

Group	Days post coitum							
	0 - 6		6 - 12		12 - 18		0 - 18	
(mg/kg)	g	(%)	g	(%)	g	(%)	g	(%)
1 (0)	19	(+7.2)	23	(+8.1)	49	(+16.0)	91	(+34.5)
2 (0.3)	22	(+8.6)	24	(+8.6)	50	(+16.6)	96	(+37.5)
3 (1.0)	22	(+8.8)	24	(+8.9)	48	(+16.3)	94	(+37.8)
4 (3.0)	21	(+8.8)	23	(+8.9)	49	(+17.4)	93	(+39.1)

Group	Days post coitum				Corrected body weight gain % # (see pp. 62-65)
	18 - 21		6 - 21		
(mg/kg)	g	(%)	g	(%)	
1 (0)	47	(+13.2)	119	(+42.0)	5.5
2 (0.3)	49	(+13.9)	123	(+44.2)	6.2
3 (1.0)	46	(+13.4)	118	(+43.5)	6.1
4 (3.0)	46	(+13.9)	118	(+45.6)	7.0

= Body weight gain at day 21 post coitum corrected for uterus weight.

Figure 112, from page 64 of — project 806916

Food consumption:
At 3 mg/kg, decreased food consumption was observed during the premating and gestation period (-14.4 and -6.95, respectively). No effects at other doses.

Toxicokinetics:
Rats were sampled on Day 14 (premating) and Gestation Day 17. Blood samples were taken at 0 (predose), 0.5, 1, 2, 4, and 8 hours post dose (3 rats/timepoint).

Comparison of toxicokinetic parameters of PAI and AI throughout the different groups after repeated administration for 14 days pre-mating and until day 17 post coitum.

Test item PAI	$AUC_{[0-t]}$ (ng*h/ml)	C_{max} (ng/ml)	T_{max} (h)	T half-life (h)	$MRT_{[last]}$ (h)
F 0.3 (14x)	92	21	0.5	1.0	1.2
F 0.3 (17 p.c.)	126	54	0.5	1.7	2.8
F 1.0 (14x)	116	60	0.5	1.2	1.7
F 1.0 (17 p.c.)	204	122	0.5	0.8	1.5
F 3.0 (14x)	351	169	0.5	1.6	2.4
F 3.0 (17 p.c.)	746	321	1.0	1.4	2.5

Test item AI	$AUC_{[0-t]}$ (ng*h/ml)	C_{max} (ng/ml)	T_{max} (h)	T half-life (h)	$MRT_{[last]}$ (h)
F 0.3 (14x)	67	15	1.0	2.9	4.4
F 0.3 (17 p.c.)	70	12	1.0	3.0	4.4
F 1.0 (14x)	241	50	1.0	3.6	5.3
F 1.0 (17 p.c.)	256	30	1.0	5.5	5.2
F 3.0 (14x)	835	193	1.0	3.4	5.2
F 3.0 (17 p.c.)	1296	214	1.0	3.7	5.0

Figure 113, from page 27 of — Project 806916

Necropsy:
No abnormal findings were noted at necropsy

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
No effects were observed on female fertility (22/22, 22/22, 21/22, 21/22 females became pregnant at 0, 0.3, 1 and 3 mg/kg, respectively). One 1 mg/kg dam delivered normal pups on GD 12, so it was assumed that the study staff had failed to detect this rat's initial mating (page 23 of the report). Thus, the number of 1 mg/kg dams in the tables below is 20 rather than 21.
No adverse effects were noted on embryo-fetal development (deaths, fetal weights)
Half of the live fetuses were examined by micro dissection for visceral abnormalities; the other half were examined for skeletal abnormalities using alizarin red S staining. No significant changes were observed in external, visceral or skeletal examinations of the fetuses.

	GROUP 1 0 MG/KG	GROUP 2 0.3 MG/KG	GROUP 3 1.0 MG/KG	GROUP 4 3.0 MG/KG
NUMBER OF DAMS	22	22	20	21
CORPORA LUTEA	354	362	320	329
MEAN (+)	16.1	16.5	16.0	15.7
ST.DEV.	2.0	1.5	1.5	2.3
PRE-IMPLANTATION LOSS	11	15	12	14
% OF CORP. LUTEA (#)	3.1	4.1	3.8	4.3
MEAN (+)	0.5	0.7	0.6	0.7
ST.DEV.	0.9	0.8	1.0	0.8
NUMBER OF DAMS AFFECTED	7	13	7	10
IMPLANTATION SITES	343	347	308	315
% OF CORP. LUTEA (#)	96.9	95.9	96.3	95.7
MEAN (+)	15.6	15.8	15.4	15.0
ST.DEV.	1.7	1.4	1.4	2.2
POST-IMPLANTATION LOSS	14	14	19	14
% OF IMPL. SITES (#)	4.1	4.0	6.2	4.4
MEAN (+)	0.6	0.6	1.0	0.7
ST.DEV.	0.6	1.0	1.3	0.9
NUMBER OF DAMS AFFECTED	13	10	12	10
IMPLANTATION SITE SCARS	0	0	0	0
EMBRYONIC/FETAL DEATHS TOTAL	14	14	19	14
EMBRYONIC RESORPTIONS	12	12	17	14
% OF IMPL. SITES (#)	3.5	3.5	5.5	4.4
MEAN (+)	0.5	0.5	0.9	0.7
ST.DEV.	0.5	0.8	1.3	0.9
NUMBER OF DAMS AFFECTED	12	9	10	10
FETAL RESORPTIONS	2	2	2	0
% OF IMPL. SITES (#)	0.6	0.6	0.6	
MEAN (+)	0.1	0.1	0.1	
ST.DEV.	0.3	0.3	0.3	
NUMBER OF DAMS AFFECTED	2	2	2	
FETUSES				
TOTAL FETUSES	329	333	289	301
% OF IMPL. SITES (#)	95.9	96.0	93.8	95.6
MEAN (+)	15.0	15.1	14.5	14.3
ST.DEV.	1.6	1.5	1.4	2.5
LIVE FETUSES	329	333	289	301
DEAD FETUSES	0	0	0	0
ABNORMAL FETUSES	1	0	1	0
% OF FETUSES (#)	0.3		0.3	
MEAN (+)	0.0		0.1	
ST.DEV.	0.2		0.2	
NUMBER OF DAMS AFFECTED	1		1	
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	1	0	1	0
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0	0	0

Figure 114, from page 72 of Project 806916

	GROUP 1 0 MG/KG	GROUP 2 0.3 MG/KG	GROUP 3 1.0 MG/KG	GROUP 4 3.0 MG/KG
NUMBER OF DAMS	22	22	20	21
SEX OF FETUSES				
TOTAL MALES	150	162	142	143
% OF FETUSES (#)	45.6	48.6	49.1	47.5
MEAN (+)	6.8	7.4	7.1	6.8
ST.DEV.	1.8	2.1	1.8	1.8
TOTAL FEMALES	179	171	147	158
% OF FETUSES (#)	54.4	51.4	50.9	52.5
MEAN (+)	8.1	7.8	7.4	7.5
ST.DEV.	1.6	2.4	2.6	2.7
LIVE MALES	150	162	142	143
LIVE FEMALES	179	171	147	158
WEIGHTS OF LIVE FETUSES (LITTER BASIS)				
TOTAL FETUSES				
N (LITTERS)	22	22	20	21
MEAN (*)	5.0	5.1	5.2	5.0
ST.DEV.	0.2	0.3	0.3	0.3
MALES				
N (LITTERS)	22	22	20	21
MEAN (*)	5.1	5.2	5.3	5.1
ST.DEV.	0.3	0.3	0.3	0.3
FEMALES				
N (LITTERS)	22	22	20	21
MEAN (*)	4.9	5.0	5.0	4.9
ST.DEV.	0.3	0.3	0.4	0.3
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)				
TOTAL FETUSES				
N (FETUSES)	329	333	289	301
MEAN (*)	5.0	5.1 **	5.1 **	5.0
ST.DEV.	0.4	0.4	0.5	0.5
MALES				
N (FETUSES)	150	162	142	143
MEAN (*)	5.1	5.2	5.3 **	5.1
ST.DEV.	0.4	0.4	0.4	0.5
FEMALES				
N (FETUSES)	179	171	147	158
MEAN (*)	4.8	5.0 *	5.0 **	4.9
ST.DEV.	0.4	0.4	0.5	0.4

Figure 115, from page 73 of Project 806916

3.4.6.3 STUDY FOR EFFECTS ON EMBRYO-FETAL DEVELOPMENT WITH RASAGILINE MESYLATE (TVP-1012) IN THE RABBIT

Key study findings:
1. 45 mg/kg caused decreased body weight in does.
2. Increased post-implantation loss was observed at 45 mg/kg.
3. Decreased fetal weight was observed at 45 mg/kg.
4. No significant increase in fetal abnormalities or variations was observed.

Study no.: — Project 671411
Location: /tox — Project 671411.pdf
Conducting laboratory and location: —
Date of study initiation: October 7, 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 255 495 223

Methods

Doses: 0, 1, 7, 45 mg/kg
Species/strain: Rabbit, Chinchilla (CHbb:CH, hybrids, SPF quality)
Number/sex/group: 20/group
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: None
Study design: Does were treated from gestation day (GD) 6 through 20; does were sacrificed on GD28 and fetuses were examined for abnormalities.
Parameters and endpoints evaluated: Embryo-fetal development

Results

Mortality (does):
0 mg/kg- Doe 5 found dead on GD26;
1 mg/kg- no deaths
7 mg/kg- Doe 54 found dead on GD28
45 mg/kg- Doe 61 found dead on GD8

Clinical signs (does):
0 mg/kg- Doe 5 had vaginal bleeding on GD25; Doe 17 partially aborted on day 28
1 mg/kg- no clinical signs
7 mg/kg- no clinical signs
45 mg/kg- Doe 61 had tachypnea, tremor and head flicking on GD7; does 62 and 76 aborted on days 27 and 20, respectively

Body weight (does):

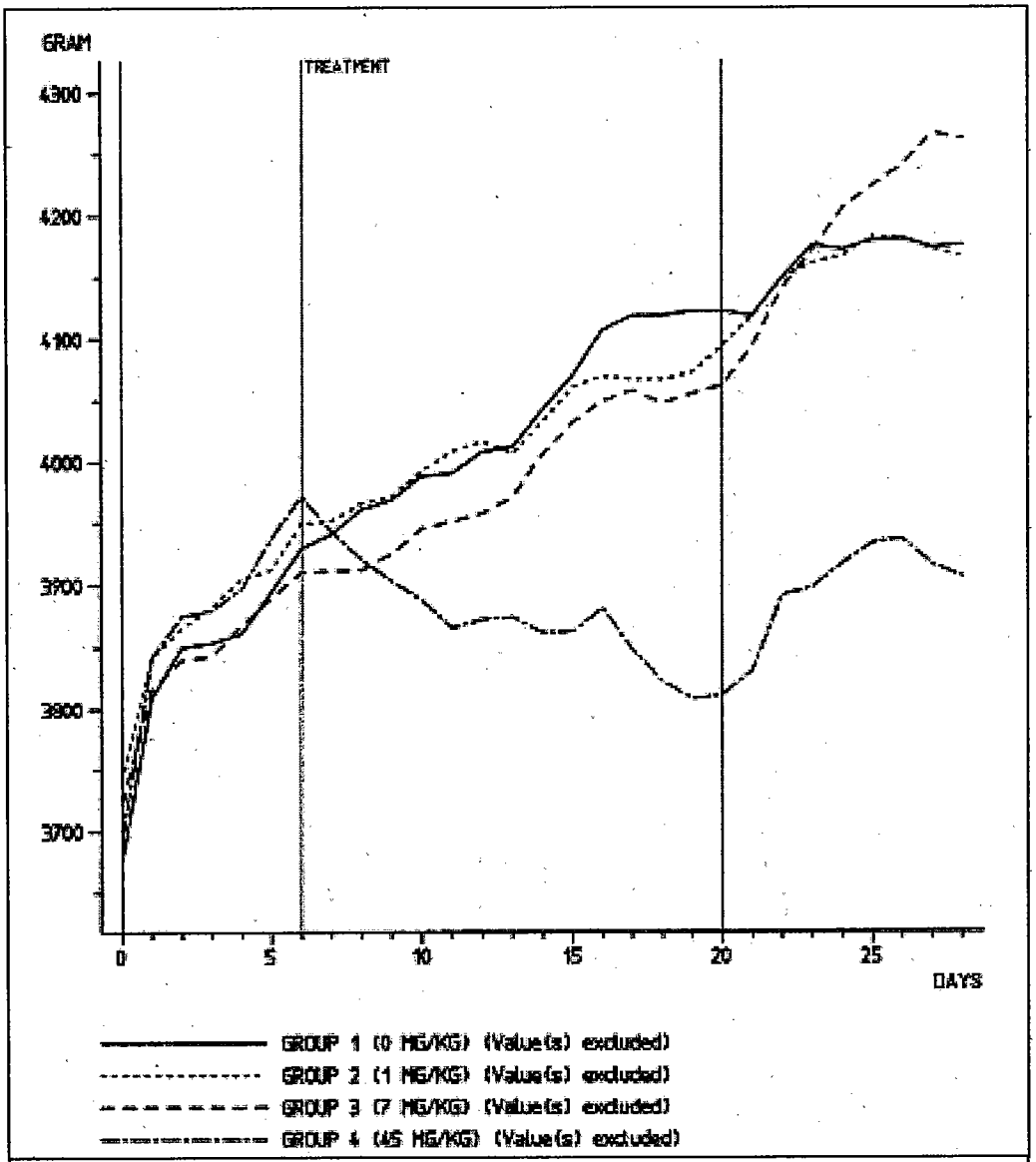

Figure 116, from page 34 of ~. Project 671411

Food consumption (does):
Decreased food consumption at 45 mg/kg (-49.6% compared to controls) during treatment

Toxicokinetics: Not done, but TK results from the dose range finding study are presented below. The doses in the dose range finding study were 5, 15 and 45 mg/kg compared to 1, 7 and 45 mg/kg in the present study.

Table 9
Pharmacokinetic parameters of PAI (base) on day 20 post coitum following daily oral administration of TVP-1012 to pregnant rabbits

Dose level (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hour)	AUC_{0-t} (ng.hour/mL)	AUC_{∞} (ng.hour/mL)
5	568.5±64.36	0.5	924.4±130.63	942.1±135.7
15	2389.9±1200.5	0.5	4461.5±1489.1	4471.0±1484.2
45	8503.3±1108.3	0.5	19186.2±4679.2	19194.6±4677.4

Table 10
Pharmacokinetic parameters of A1 (base) on day 20 post coitum following daily oral administration of TVP-1012 to pregnant rabbits

Dose level (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hour)	AUC_{0-t} (ng.hour/mL)	AUC_{∞} (ng.hour/mL)
5	50.70±11.18	0.75±0.29	115.0±22.77	125.67±28.73
15	326.3±119.3	0.80±0.27	1008.9±470.7	1062.52±496.2
45	1454.7±195.3	0.67±0.29	5448.8±2574.9	5610.12±2443.1

Figure 117, from page 34 of Report PK101/98

Terminal and necroscopic evaluations:C-section data (implantation sites, pre- and post-implantation loss, etc.):

	GROUP 1 0 MG/KG	GROUP 2 1 MG/KG	GROUP 3 7 MG/KG	GROUP 4 49 MG/KG
NUMBER OF DAMS	16	19	18	18
CORPORA LUTEA	165	197	190	188
MEAN (+)	10.3	10.4	10.6	10.4
ST.DEV.	1.7	1.9	1.8	1.4
PRE-IMPLANTATION LOSS	13	5	4	2
% OF CORP. LUTEA (#)	7.9	2.5 #	2.1 #	1.1 ##
MEAN (+)	0.8	0.3	0.2	0.1
ST.DEV.	1.1	0.6	0.4	0.3
NUMBER OF DAMS AFFECTED	7	4	4	2
IMPLANTATION SITES	152	192	186	186
% OF CORP. LUTEA (#)	92.1	97.5 #	97.9 #	98.9 ##
MEAN (+)	9.5	10.1	10.3	10.3
ST.DEV.	2.2	1.8	2.0	1.4
POST-IMPLANTATION LOSS	20	21	10	38
% OF IMPL. SITES (#)	13.2	10.9	5.4 #	20.4
MEAN (+)	1.3	1.1	0.6	2.1
ST.DEV.	2.3	2.2	0.7	3.7
NUMBER OF DAMS AFFECTED	7	7	6	9
IMPLANTATION SITE SCARS	9	0	0	30
% OF IMPL. SITES (#)	5.9			16.1 ##
MEAN (+)	0.6			1.7
ST.DEV.	2.3			3.9
EMBRYONIC/FETAL DEATHS TOTAL	11	21	10	8
% OF IMPL. SITES (#)	7.2	10.9	5.4	4.3
MEAN (+)	0.7	1.1	0.6	0.4
ST.DEV.	1.0	2.2	0.7	0.8
NUMBER OF DAMS AFFECTED	6	7	6	6
EMBRYONIC RESORPTIONS	9	5	4	4
% OF IMPL. SITES (#)	5.9	2.6	2.2	2.2
MEAN (+)	0.6	0.3	0.2	0.2
ST.DEV.	1.0	0.7	0.4	0.7
NUMBER OF DAMS AFFECTED	5	3	3	2
FETAL RESORPTIONS	2	16	6	4
% OF IMPL. SITES (#)	1.3	8.3 ##	3.2	2.2
MEAN (+)	0.1	0.8	0.3	0.2
ST.DEV.	0.5	2.1	0.7	0.6
NUMBER OF DAMS AFFECTED	1	5	4	4
FETUSES				
TOTAL FETUSES	132	171	176	148
% OF IMPL. SITES (#)	86.8	89.1	94.6 #	79.6
MEAN (+)	8.3	9.0	9.8	8.2
ST.DEV.	3.3	2.3	1.8	4.0
LIVE FETUSES	132	171	176	148
DEAD FETUSES	0	0	0	0
ABNORMAL FETUSES	2	1	0	0
% OF FETUSES (#)	1.5	0.6		
MEAN (+)	0.1	0.1		
ST.DEV.	0.3	0.2		
NUMBER OF DAMS AFFECTED	2	1		
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	2	1	0	0
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0	0	0

+/++ : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

Figure 118, from page 61 of Project 671411

	GROUP 1 0 MG/KG	GROUP 2 1 MG/KG	GROUP 3 7 MG/KG	GROUP 4 45 MG/KG
NUMBER OF DAMS	16	19	18	15
SEX OF FETUSES				
TOTAL MALES	62	88	93	72
% OF FETUSES (#)	47.3	51.5	52.5	48.6
MEAN (+)	3.9	4.6	5.1	4.8
ST.DEV.	2.3	1.7	1.6	2.0
TOTAL FEMALES	70	83	84	76
% OF FETUSES (#)	53.0	48.5	47.7	51.4
MEAN (+)	4.4	4.4	4.7	4.2
ST.DEV.	2.3	1.6	1.4	2.4
LIVE MALES	62	86	92	72
LIVE FEMALES	70	83	84	76
WEIGHTS OF LIVE FETUSES (LITTER BASIS)				
TOTAL FETUSES				
N (LITTERS)	15	19	18	15
MEAN (*)	34.8	33.3	33.5	30.1
ST.DEV.	11.3	4.6	4.6	16.5
MALES				
N (LITTERS)	14	19	18	15
MEAN (*)	34.3	33.3	33.7	30.4 *
ST.DEV.	5.9	4.4	4.6	4.1
FEMALES				
N (LITTERS)	15	19	18	15
MEAN (*)	34.9	33.5	33.4	29.7 *
ST.DEV.	7.6	4.9	4.9	4.9
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)				
TOTAL FETUSES				
N (FETUSES)	132	171	176	148
MEAN (*)	33.7	33.6	33.8	29.9 **
ST.DEV.	7.1	5.3	5.7	5.2
MALES				
N (FETUSES)	62	88	92	72
MEAN (*)	34.2	33.3	33.8	30.4 **
ST.DEV.	6.6	5.1	5.3	5.2
FEMALES				
N (FETUSES)	70	83	84	76
MEAN (*)	33.2	33.7	33.8	29.4 **
ST.DEV.	7.5	5.9	6.0	5.1

Figure 119, from page 62 of Project 671411

45 mg/kg- Increased post-implantation loss due in part to 3 does having complete resorptions or abortions.

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Offspring (malformations, variations, etc.):
Decreased fetal weight was observed at 45 mg/kg.
No significant increases in abnormalities or variations.

External and Fresh Visceral Examinations of Fetuses

Group (mg/kg)	No. of fetuses examined	Type of abnormal finding	Individual data of fetus(es)*	Fetus(es) of litter number
1 (0)	132	(ex) Arthrogryposis (left and right forepaw)	91/19.6/F	4
		(ex) Oligodactylia, claws partially missing (left forepaw)	294/40.7/M	11
2 (1)	171	(ex) Arthrogryposis (left and right forepaw)	252/20.8/M	29
3 (7)	176	No abnormal findings		
4 (45)	148	(ex) Fontanelle moderately enlarged	287/22.8/M	69
		(ex) Fontanelle slightly enlarged	423/24.1/F	72

* = Fetus number / body weight in grams / sex (M = male; F = female)
(ex) = External examination including examination of the cranium for the degree of ossification after the skin had been removed.

Figure 120, from page 71 of Project 671411

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Examination of Heads, Including Brain of Fetuses (by Wilson Technique")**

Group (mg/kg)	No. of heads examined	Type of abnormal finding	Individual data of fetus(es)*	Fetus(es) of litter number
1 (0)	132	Hydrocephalus internus (both hemisphaeres)	91/19.6/F	4
2 (1)	171	No abnormal findings		
3 (7)	176	No abnormal findings		
4 (45)	148	No abnormal findings		

* = Fetus number / body weight in grams / sex (M = male; F = female)

Figure 121, from page 72 of — Report 671411

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Skeletal Examination of Fetuses (Abnormal Findings)

Group (mg/kg)	No. of fetuses examined	Type of abnormal finding	Individual data of fetus(es)	Fetus(es) of litter number
1 (0)	132	Rib no. 13, flying (both sides) Sternebrae nos. 4 and 5 abnormally ossified and fused.	442/36.3/M	15
		Oligodactylia, claws partially missing (left forepaw) (confirmation of the findings noted during the external examination, see page 71)	294/40.7/M	11
2 (1)	171	11^{th} thoracic vertebral arch and 11^{th} rib missing (right side), 11^{th} and 12^{th} thoracic vertebral body fused (left side)	53/38.8/F	23
3 (7)	176	10^{th} thoracic vertebral body and 10^{th} thoracic vertebral arch (right side) missing, rib no. 10 flying, 10^{th} and 11^{th} thoracic vertebral arches (left) fused	335/35.4/F	50
4 (45)	148	11^{th} thoracic vertebral body and 11^{th} thoracic vertebral arch (right side) missing, ribs nos. 11 and 12 (right side) basal fused	359/38.3/M	70

* = Fetus number / body weight in grams / sex (M = male; F = female)

Figure 122, from page 73 of — Project 671411

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3.4.6.4 STUDY ON THE COMBINED EFFECTS OF RASAGILINE MESYLATE (TVP-1012) AND LEVODOPA/CARBIDOPA (80/20 MG/KG/DAY) ON EMBRYO-FETAL DEVELOPMENT AFTER ORAL ADMINISTRATION IN THE RAT

Key study findings:
1. Combination of rasagiline (up to 1 mg/kg) with sinemet (80 mg/kg levdopa/20 mg/kg carbidopa) did not increase the incidence of fetal abnormalities.
2. Slight maternal toxicity was observed at the high dose combination as indicated by slightly reduced dam weight and increased skeletal variations.

Study no.: — Project 817806
Study Location: /tox/ — Project 817806.pdf
Conducting laboratory and location: —
Date of study initiation: November 28, 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 255400100 —
Methods

Doses:

Group	Female Numbers Main Study	Female Numbers Toxico-kinetic Study	Test items and dose* mg/kg	
1	1 - 22	133 - 135	Methyl cellulose:	5 ml/kg (in the morning) 5 ml/kg (in the afternoon)
2	23 - 44	136 - 144	Rasagiline: Methylcellulose:	1 mg/kg (in the morning) 5 ml/kg (in the afternoon)
3	45 - 66	145 - 153	LD**/CD***:	40/10 mg/kg (in the morning) 40/10 mg/kg (in the afternoon)
4	67 - 88	154 - 162	LD**/CD***:	40/10 mg/kg + 0.1 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —
5	89 - 110	163 - 171	LD**/CD***:	40/10 mg/kg + 0.3 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —
6	111 - 132	172 - 180	LD**/CD***:	40/10 mg/kg + 1 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —

* = Dose levels were based on results of RCC study number 817795, in which a dose level of 3 mg/kg Rasagiline (TVP-1012) and Levodopa/Carbidopa 80/20 mg/kg caused severe symptoms and mortalities.
** = LEVODOPA
*** = CARBIDOPA

Figure 123, from page 26 of — Project 817806

Species/strain: Rat Icolbm: OFA Sprague-Dawley SPF
Number/sex/group: 22 females/group
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: 9 rats/dose
Study design: Pregnant rats were dosed from Gestation Day (GD) 8 through 17. Dosing was initiated on GD8 rather than GD6 due to the known effects of dopamine agonists (e.g. levodopa) on implantation in rats. Dams were sacrificed on GD21.

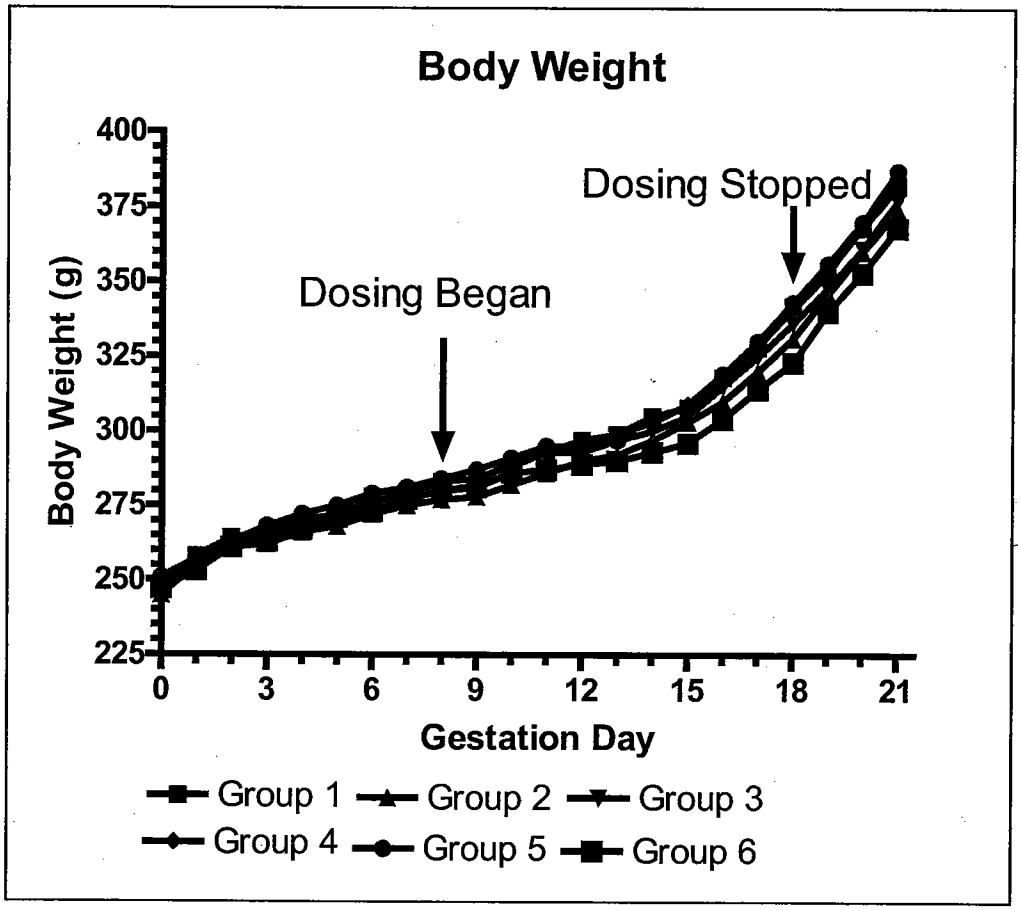
Parameters and endpoints evaluated: effects on embryo-fetal development Half of the live fetuses were examined by micro dissection for visceral abnormalities; the other half were examined for skeletal abnormalities using alizarin red S staining.

Results

Mortality (dams):
At 1 mg/kg rasagiline alone, 1 rat was found dead on GD20. No clinical signs or symptoms of ill health were noted in this rat or others in this group. This death was not considered drug related.

Clinical signs (dams):
All levodopa/carbidopa treated rats had ruffled fur.
No clinical signs were observed in rats administered rasagiline alone.

Body weight (dams):



Food consumption (dams):
Decreased food consumption during GD8-12 was observed in groups 5 and 6 (-6.3 and -14.6%, respectively).

Toxicokinetics:

PAI

Group(s)	C_{max} (ng/ml)	T_{max} (h)	$AUC_{(0-t)}$ (ng h/ml)	T half life (h)	MRT (h)
2	77 (100%)	0.5	136 (100%)	0.7	2.6
5**	12	0.5	41	1.2	2.6
6	38 (49%)	0.5	95 (70%)	1.8	4.2

AI

Group(s)	C_{max} (ng/ml)	T_{max} (h)	$AUC_{(0-t)}$ (ng h/ml)	T half life (h)	MRT (h)
2	43 (100%)	1.0	241 (100%)	6.0	8.8
6	25 (58%)	4.0	161 (67%)	*	16.6

$AUC_{(0-t)}$: t was 8 hours

* = No reliable value due to lack of sufficient data for calculation (see table 4 p. 585)

** = Not used for interpretation

Figure 124, from page 32 of — Project 817806

LD

Group	C_{max} (ng/ml)	T_{max} (h)	$AUC_{(0-t)}$ (ng h/ml)	T half life (h)	MRT (h)
3	3228 (100%)	1.0	8596 (100%)	1.8	2.8
4	2719 (84%)	1.0	7529 (87%)	2.2	3.3
5	2263 (70%)	0.5	7160 (83%)	2.7	4.1
6	2318 (72%)	0.5	8835 (102%)	2.4	3.6

CD

Group	C_{max} (ng/ml)	T_{max} (h)	$AUC_{(0-t)}$ (ng h/ml)	T half life (h)	MRT (h)
3	357 (100%)	1.0	957 (100%)	*	2.4
4	289 (81%)	1.0	779 (81%)	1.3	2.0
5	222 (62%)	1.0	703 (73%)	1.6	2.1
6	257 (72%)	0.5	743 (76%)	2.2	2.2

$AUC_{(0-t)}$: t was 8 hours

* = No reliable value due to lack of sufficient data for calculation (see table 9 p. 589)

Figure 125, from page 33 of — Project 817806

Terminal and necroscopic evaluations:C-section data (implantation sites, pre- and post-implantation loss, etc.):

No adverse effects on necropsy

	GROUP 1 0 MG/KG	GROUP 2 1.6 MG/KG.	GROUP 3 80/16 LD/CD	GROUP 4 80/20+8.1 LD/CD+MG/KG.	GROUP 5 80/20+0.3 LD/CD+MG/KG.
NUMBER OF DAMS	20	20	20	20	21
CORPORA LUTEA	323	330	312	333	361
MEAN (+)	16.2	16.5	15.6	16.7	16.2
ST.DEV.	1.7	1.3	3.4	2.0	2.5
PRE-IMPLANTATION LOSS	12	16	21	14	25
% OF CORP. LUTEA (#)	3.7	4.8	6.7	4.1	7.1 #
MEAN (+)	0.6	0.9	1.1	0.8	1.2 +
ST.DEV.	0.8	1.4	1.2	0.8	0.8
NUMBER OF DAMS AFFECTED	9	10	12	12	17
IMPLANTATION SITES	311	313	291	299	336
% OF CORP. LUTEA (#)	96.3	94.5	93.3	89.9	92.7 #
MEAN (+)	15.6	15.6	14.8	14.9	15.0 +
ST.DEV.	1.5	1.8	2.8	2.3	2.2
POST-IMPLANTATION LOSS	17	13	31	17	14
% OF IMPL. SITES (#)	5.5	4.2	9.1	5.7	4.4
MEAN (+)	0.9	0.7	1.1	0.8	0.7
ST.DEV.	1.4	0.8	1.3	1.4	1.0
NUMBER OF DAMS AFFECTED	11	9	12	11	9
IMPLANTATION SITE SCARS	0	0	0	0	0
EMBRYONIC/FETAL DEATHS TOTAL	17	13	21	17	14
EMBRYONIC RESORPTIONS	16	12	19	17	13
% OF IMPL. SITES (#)	5.1	3.8	6.5	5.7	4.1
MEAN (+)	0.8	0.6	1.0	0.9	0.6
ST.DEV.	1.1	0.8	1.1	1.0	1.0
NUMBER OF DAMS AFFECTED	10	8	11	11	8
FETAL RESORPTIONS	1	1	2	0	1
% OF IMPL. SITES (#)	0.3	0.3	0.7		0.3
MEAN (+)	0.1	0.1	0.1		0.0
ST.DEV.	0.3	0.3	0.4		0.2
NUMBER OF DAMS AFFECTED	1	1	1		1
FETUSES					
TOTAL FETUSES	294	299	270	280	322
% OF IMPL. SITES (#)	94.5	95.5	92.8	94.3	95.6
MEAN (+)	14.7	15.0	13.5	14.0	14.4
ST.DEV.	1.6	1.7	2.9	2.5	1.7
LIVE FETUSES	294	299	270	280	322
DEAD FETUSES	0	0	0	0	0
ABNORMAL FETUSES	0	0	0	0	1
% OF FETUSES (#)					0.3
MEAN (+)					0.0
ST.DEV.					0.2
NUMBER OF DAMS AFFECTED					1
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	0	0	0	0	1
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0	0	0	0

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

Figure 126, from page 88 of — roject 817806

	GROUP 1 0 MG/KG	GROUP 2 1.0 MG/KG.	GROUP 3 80/26 LD/CD	GROUP 4 80/20+0.1 LD/CD+MG/KG.	GROUP 5 80/20+0.3 LD/CD+MG/KG.
NUMBER OF DAMS	20	20	20	20	21
SEX OF FETUSES					
TOTAL MALES	156	147	128	137	156
% OF FETUSES (M)	53.1	49.2	47.4	48.9	53.7
MEAN (+)	7.8	7.4	6.4	6.8	7.4
ST.DEV.	1.9	2.0	2.0	1.8	2.1
TOTAL FEMALES	138	152	142	143	146
% OF FETUSES (F)	46.9	50.8	52.6	51.1	48.3
MEAN (+)	6.9	7.6	7.1	7.2	7.0
ST.DEV.	1.7	1.8	2.5	2.5	2.0
LIVE MALES	154	147	128	137	156
LIVE FEMALES	138	152	142	143	146
WEIGHTS OF LIVE FETUSES (LITTER BASIS)					
TOTAL FETUSES					
N (LITTERS)	20	20	20	20	21
MEAN (+)	5.2	5.1	5.1	5.2	5.3
ST.DEV.	0.2	0.3	0.3	0.3	0.3
MALES					
N (LITTERS)	20	20	20	20	21
MEAN (+)	5.3	5.3	5.3	5.3	5.4
ST.DEV.	0.2	0.3	0.3	0.2	0.3
FEMALES					
N (LITTERS)	20	20	20	20	21
MEAN (+)	5.0	5.0	5.0	5.1	5.1
ST.DEV.	0.3	0.2	0.5	0.2	0.2
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)					
TOTAL FETUSES					
N (FETUSES)	294	299	270	280	302
MEAN (+)	5.2	5.1	5.1 *	5.2	5.3 *
ST.DEV.	0.4	0.4	0.5	0.4	0.4
MALES					
N (FETUSES)	156	147	128	137	156
MEAN (+)	5.3	5.3	5.2	5.3	5.4 *
ST.DEV.	0.4	0.3	0.4	0.4	0.4
FEMALES					
N (FETUSES)	138	152	142	143	146
MEAN (+)	5.1	5.0	4.9	5.1	5.1
ST.DEV.	0.4	0.4	0.5	0.4	0.3

Figure 127, from page 89 of — Project 817806

	GROUP 1 0 MG/KG	GROUP 6 80/30+1.0 LD/CD+RABAG.
NUMBER OF DAMS	20	22
CORPORA LUTEA	323	337
MEAN (+)	16.2	15.3
ST.DEV.	1.7	2.3
PRE-IMPLANTATION LOSS	12	22
% OF CORP. LUTEA (#)	3.7	6.5
MEAN (+)	0.6	1.0
ST.DEV.	0.8	1.0
NUMBER OF DAMS AFFECTED	9	14
IMPLANTATION SITES	311	315
% OF CORP. LUTEA (#)	96.3	93.5
MEAN (+)	15.6	14.3
ST.DEV.	1.5	2.6
POST-IMPLANTATION LOSS	17	11
% OF IMPL. SITES (#)	5.5	3.5
MEAN (+)	0.9	0.5
ST.DEV.	1.1	1.1
NUMBER OF DAMS AFFECTED	11	6
IMPLANTATION SITE SCARS	0	0
EMBRYONIC/FETAL DEATHS TOTAL	17	11
EMBRYONIC RESORPTIONS	16	9
% OF IMPL. SITES (#)	5.1	2.9
MEAN (+)	0.8	0.4
ST.DEV.	1.1	1.2
NUMBER OF DAMS AFFECTED	10	4
FETAL RESORPTIONS	1	2
% OF IMPL. SITES (#)	0.3	0.6
MEAN (+)	0.1	0.1
ST.DEV.	0.3	0.3
NUMBER OF DAMS AFFECTED	1	2
FETUSES		
TOTAL FETUSES	294	304
% OF IMPL. SITES (#)	94.3	96.5
MEAN (+)	14.7	13.8
ST.DEV.	1.6	2.4
LIVE FETUSES	294	304
DEAD FETUSES	0	0
ABNORMAL FETUSES	0	0
% OF FETUSES (#)		
MEAN (+)		
ST.DEV.		
NUMBER OF DAMS AFFECTED		
ABNORMAL LIVE FETUSES AT EXTERNAL EXAMINATION	0	0
ABNORMAL DEAD FETUSES AT EXTERNAL EXAMINATION	0	0

*/** : Dunnett-Test based on pooled variance significant at level 5% (*) or 1% (**)
#/## : Fisher's Exact Test significant at level 5% (#) or 1% (##)
+ : Steel Test significant at level 5%

Figure 128, from page 90 of — Project 817806

	GROUP 1 0 MG/KG	GROUP 6 80/20+1.0 LD/CD+RASAG.
NUMBER OF DAMS	20	22
SEX OF FETUSES		
TOTAL MALES	156	151
% OF FETUSES (#)	53.1	49.7
MEAN (+)	7.8	6.9
ST.DEV.	1.3	1.8
TOTAL FEMALES	138	153
% OF FETUSES (#)	46.9	50.3
MEAN (+)	6.9	7.0
ST.DEV.	1.7	2.1
LIVE MALES	156	151
LIVE FEMALES	138	153
WEIGHTS OF LIVE FETUSES (LITTER BASIS)		
TOTAL FETUSES		
N (LITTERS)	20	22
MEAN (*)	5.2	5.2
ST.DEV.	0.2	0.4
MALES		
N (LITTERS)	20	22
MEAN (*)	5.3	5.3
ST.DEV.	0.2	0.4
FEMALES		
N (LITTERS)	20	22
MEAN (*)	5.0	5.1
ST.DEV.	0.3	0.4
WEIGHTS OF LIVE FETUSES (INDIVIDUAL BASIS)		
TOTAL FETUSES		
N (FETUSES)	294	304
MEAN (*)	5.2	5.1
ST.DEV.	0.4	0.5
MALES		
N (FETUSES)	156	151
MEAN (*)	5.3	5.3
ST.DEV.	0.4	0.5
FEMALES		
N (FETUSES)	138	153
MEAN (*)	5.1	5.0
ST.DEV.	0.4	0.4

Figure 129, from page 91 of — Project 817806

Offspring (malformations, variations, etc.):
No effects on fetal body weight.
One group 5 fetus had scoliosis and kyphosis with a hindlimb medially rotated and stretched.
No significant incidence of visceral or skeletal abnormalities were observed.
There were occasional increases in the incidence of skeletal variations (incomplete ossification), which are generally indicative of maternal toxicity.

VISCERAL EXAMINATION OF FETUSES BY MICRODISSECTION TECHNIQUE - SUMMARY OF FINDINGS

Group Dose (mg/kg/day)	1 (0)		2 (1.0) (Ras)		3 (80/20) (LD/CD)	
Number of litters	20		20		20	
Number of fetuses examined	153		154		141	
Incidences of fetuses with	N	%	N	%	N	%
Abnormality(ies) of heart trunk vessels	2	1	0	0	1	1
Thymus elongated (bi-/unilateral)	8	5	7	5	10	7
Localized haemorrhage	24	16	11	7	16	11
Small additional liver lobe within the median cleft	26	17	26	17	28	20
Median liver lobe with displaced cleft	0	0	3	2	5	4
Renal pelvis(es) dilated	23	15	21	14	25	18
Left-sided umbilical artery	0	0	4	3	3	2
Other abnormalities	7	5	0	0	2	1
Litters with any abnormal finding	20	100	18	90	19	95
Fetuses with any abnormal finding	69	45	61	40	74	52

Figure 130, form page 99 of — Project 817806

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VISCERAL EXAMINATION OF FETUSES BY MICRODISSECTION TECHNIQUE - SUMMARY OF FINDINGS

Group Dose (mg/kg/day)	4 (80/20+0.1) (LD/CD + Ras)		5 (80/20+0.3) (LD/CD + Ras)		6 (80/20+1.0) (LD/CD + Ras)	
Number of litters	20		21		22	
Number of fetuses examined	145		156		158	
Incidences of fetuses with	N	%	N	%	N	%
Abnormality(ies) of heart trunk vessels	0	0	1	1	0	0
Thymus elongated (bi-/unilateral)	10	7	6	4	10	6
Localized haemorrhage	14	10	15	10	13	8
Small additional liver lobe within the median cleft	26	18	31	20	22	14
Median liver lobe with displaced cleft	5	3	6	4	8	5
Renal pelvis(es) dilated	13	9	12	8	7	4
Left-sided umbilical artery	4	3	2	1	1	1
Other abnormalities	4	3	0	0	1	1
Litters with any abnormal finding	19	95	20	95	21	95
Fetuses with any abnormal finding	65	45	61	39	53	34

Figure 131, from page 100 of ⌐ Project 817806

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SKELETAL EXAMINATION OF FETUSES - ABNORMAL FINDINGS AND SKELETAL VARIANTS

Group (mg/kg)	No. of Fetuses examined	Type of abnormal finding	Litter No.	Fetus No.
1 (0)	141	Thoracic vertebral body 12 dumbbell-shaped	2	273
		Thoracic vertebral body 12 dumbbell-shaped	3	291
		Thoracic vertebral body 11 dumbbell-shaped	3	297
		Thoracic vertebral body 13 bipartite	6	915
		Thoracic vertebral body 11 slightly dumbbell-shaped	16	1206
		Thoracic vertebral body 12 slightly dumbbell-shaped	18	1370
2 (1.0)	145	Thoracic vertebral body 12 slightly dumbbell-shaped	25	182
		Thoracic vertebral body 11 slightly dumbbell-shaped	26	204
		Thoracic vertebral body 11 slightly dumbbell-shaped	35	854
		Thoracic vertebral body 12 bipartite	44	1475
3 (80/20)	129	Thoracic vertebral body 11 dumbbell-shaped	48	228
		Thoracic vertebral bodies 11 and 13 dumbbell-shaped	48	232
		Thoracic vertebral bodies 10 and 11 slightly dumbbell-shaped	48	236
		Thoracic vertebral body 12 dumbbell-shaped	48	238
		Thoracic vertebral body 12 dumbbell-shaped	52	677
		Thoracic vertebral body 12 bipartite	58	1241
		Sternebra 6 bipartite, thoracic vertebral bodies 10 and 12 right portions absent, lumbar vertebral body 1 right portion absent	63	1616
		Thoracic vertebral body 9 dumbbell-shaped	63	1624

Figure 132, from page 118 of — Project 817806

SKELETAL EXAMINATION OF FETUSES - ABNORMAL FINDINGS AND SKELETAL VARIANTS

Group (mg/kg)	No. of Fetuses examined	Type of abnormal finding	Litter No.	Fetus No.
4 (80/20+0.1)	135	Thoracic vertebral body 12 dumbbell-shaped	71	415
		Thoracic vertebral body 9 dumbbell-shaped	71	421
		Thoracic vertebral body 12 dumbbell-shaped	72	716
		Thoracic vertebral body 11 dumbbell-shaped	73	718
		Thoracic vertebral body 11 dumbbell-shaped	73	724
		Thoracic vertebral body 11 dumbbell-shaped	74	733
		Thoracic vertebral body 11 bipartite	82	1306
		Thoracic vertebral body 11 slightly dumbbell-shaped	86	1517
		Thoracic vertebral body 12 dumbbell-shaped	86	1527
5 (80/20+0.3)	146	Left ribs 6 - 12 wavy, 10 slightly shortened, right ribs 5 - 9 wavy	90	94
		Thoracic vertebral body 12 slightly dumbbell-shaped	94	436
		Thoracic vertebral body 11 dumbbell-shaped	94	440
		Thoracic vertebral body 11 slightly dumbbell-shaped	98	494
		Thoracic vertebral body 13 dumbbell-shaped	98	504
		Thoracic vertebral body 11 markedly dumbbell-shaped	98	506
		Thoracic vertebral body 11 dumbbell-shaped	103	1149
		Thoracic vertebral body 11 dumbbell-shaped	104	1163

Figure 133, from page 119 of – *P*roject 817806

SKELETAL EXAMINATION OF FETUSES - ABNORMAL FINDINGS AND SKELETAL VARIANTS

Group (mg/kg)	No. of Fetuses examined	Type of abnormal finding	Litter No.	Fetus No.
6 (80/20+1.0)	146	Thoracic vertebral body 12 slightly dumbbell-shaped	114	158
		Left ribs 8 and 10 - 12 slightly wavy, right ribs 10 - 13 wavy	118	544
		Left ribs 11 and 12 slightly wavy, right ribs 7 slightly wavy, 8 - 12 wavy	118	546
		Right ribs 10 and 11 slightly wavy	118	548
		Left ribs 10 - 12 wavy, right ribs 9 - 12 wavy	118	552
		Left ribs 10 - 12 wavy, right ribs 5 and 6 slightly wavy, 7 - 12 wavy	118	554
		Left ribs 10 and 11 slightly wavy, right ribs 9 - 12 wavy	120	817
		Thoracic vertebral body 10 bipartite	127	1195
		Thoracic vertebral body 13 dumbbell-shaped	128	1326
		Right ribs 10 - 12 slightly wavy	129	1339
		Right ribs 11 and 12 wavy	129	1341
		Left ribs 11 and 12 slightly wavy, right ribs 6 - 8 slightly wavy, 9 - 13 wavy	129	1345
		Thoracic vertebral body 13 dumbbell-shaped	129	1347
		Right ribs 11 and 12 slightly wavy	129	1351

Figure 134, from page 120 of ~ Project 817806

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3.4.6.5 STUDY ON THE COMBINED EFFECTS OF RASAGILINE MESYLATE (TVP-1012) AND LEVODOPA/CARBIDOPA (80/20 MG/KG/DAY) ON EMBRYO-FETAL DEVELOPMENT AFTER ORAL ADMINISTRATION IN THE RABBIT

Key study findings:
1. Rabbits did not tolerate the combination of 3 mg/kg rasagiline with 80/20 mg/kg levodopa/carbidopa.
2. The combination of 0.6 or 1.2 mg/kg rasagiline with 80/20 mg/kg levodopa/carbidopa caused an increased rate of total implant loss.
3. No other adverse effects were observed on embryo-fetal development.

Study no.: — Project 826468
Location: /tox/ — Project 826468.pdf
Conducting laboratory and location: —
Date of study initiation: January 29, 2002
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 255400100 —
Methods

Group	Female Numbers	Test items and dose mg/kg	
1	1 - 22	Methyl cellulose:	5 ml/kg (in the morning) 5 ml/kg (in the afternoon)
2	23 - 44	Rasagiline: Methylcellulose:	3 mg/kg (in the morning) 5 ml/kg (in the afternoon)
3	45 - 66	LD*/CD**:	40/10 mg/kg (in the morning) 40/10 mg/kg (in the afternoon)
4	67 - 88	LD*/CD**:	40/10 mg/kg + 0.1 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —
5	89 - 110	LD*/CD**:	40/10 mg/kg + 0.6 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —
6	123 - 144***	LD*/CD**:	40/10 mg/kg + 1.2 mg/kg Rasagiline (in the morning) 40/10 mg/kg (in the afternoon) —

* = LEVODOPA
** = CARBIDOPA
*** Re-allocation of animal numbers of group 6 was specified in the amendment no. 2 to the study plan

Figure 135, from page 19 of — Project 826468

Doses:
Species/strain: Rabbit, Chinchilla
Number/sex/group: 22/dose
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: Not done
Study design: Rabbits were dosed from Gestation Day (GD) 6-18; they were sacrificed on GD28
Parameters and endpoints evaluated: Embryo-fetal development

Results

Mortality (dams):
The original high combination dose (3 mg/kg rasagiline/100 mg/kg sinemet) resulted in excessive maternal toxicity (13 animals died or were sacrificed moribund). A separate high dose group was initiated for the study.

Group	1	2	3	4	5	6
Number of mated females	22	22	22	22	22	22
Female numbers	1-22	23-44	45-66	67-88	89-110	123-144
Number of pregnant females	20	21	21	22	20	22
Died/moribund sacrifice (A)	2	2	1	2	1	2
Accidental death (B)	0	1	0	0	1	0
Killed after abortion (C)	1	2	0	0	3	0
Examined at C-section	19	17	21	20	18	20
Non pregnant (D)	2	1	1	0	2	0
Showing total post-implantation loss (E)	0	0	1	1	3	4
Number of females with live fetuses at termination*	17	16	19	19	13	16

* = Used for calculation of group mean values for food consumption and body weight data.

Figure 136, from page 27 of — Project 826468

Clinical signs (dams):
No particular signs were associated with treatment.

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Body weight (dams): Decreased body weight was observed in all groups after Gd6; the decreases in groups 4 (-80g), 5 (-85 g) and 6 (-112 g) were much higher than control decreases (-42g) and were considered treatment related. The decreases in groups 2 (-65 g) and 3 (-31 g) were less and not considered dose related.

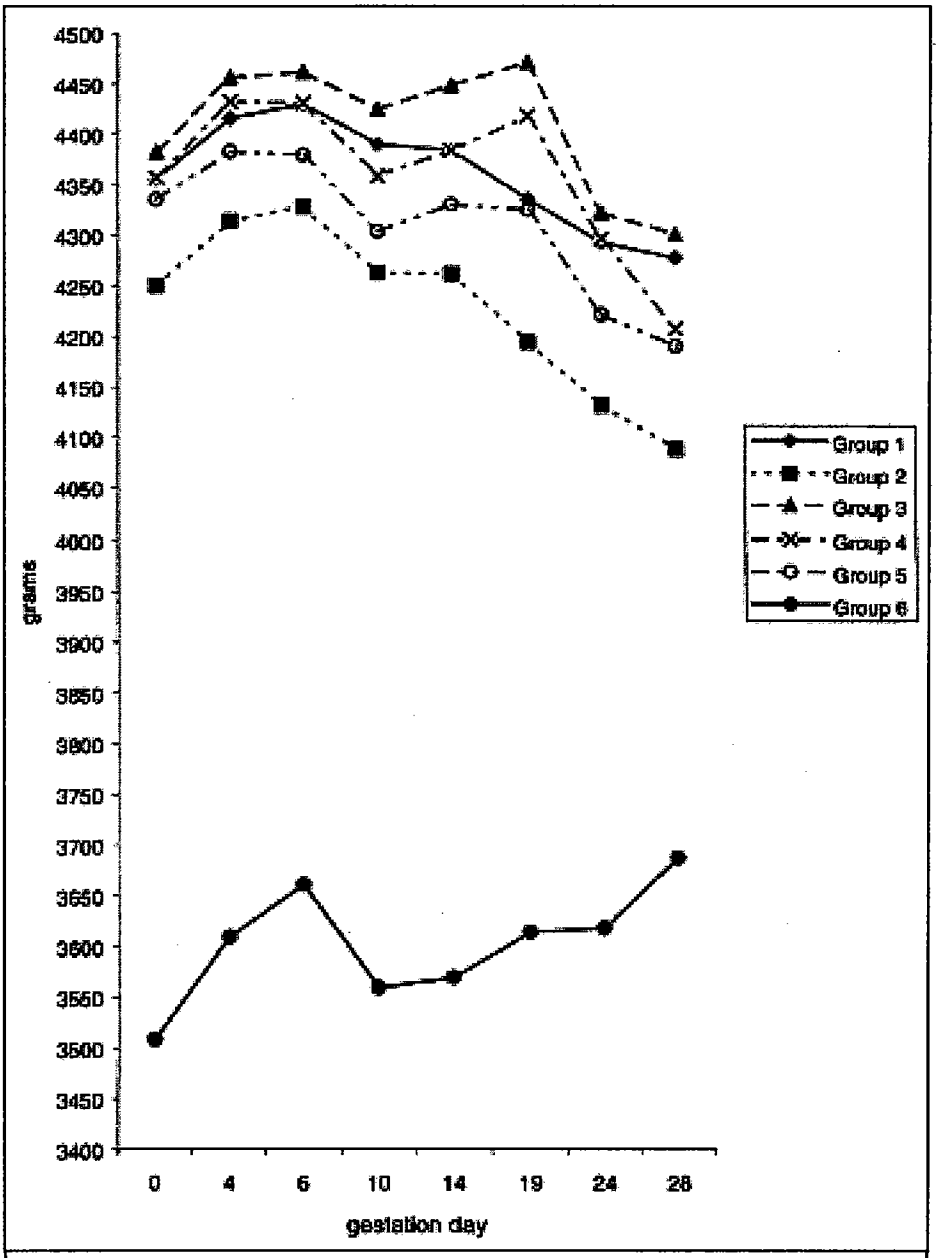

Figure 137, from page 42 of — Project 826468

Food consumption (dams):
Decreased food consumption was observed in groups 4, 5 and 6.

Toxicokinetics:

PAI	$AUC_{(0-t)}$ (ng·h/mL)	Dose normalized $AUC_{(0-t)}$* (ng·h/mL)	Cmax (ng/mL)	Dose normalized Cmax** (ng/mL)	Tmax (h)	t½ (h)	$MRT_{(po-po)}$ (h)
Group 2: 3_Rasagiline	400	133 (100 %)	183	61.0 (100 %)	1.2	2.1	3.8
Group 4: 0.1_Rasagiline/LD/CD	15.7	157 (118 %)	5.5	55.0 (90 %)	0.8	2.4	2.1
Group 5: 0.6_Rasagiline/LD/CD	91.2	152 (114 %)	27.4	45.7 (75 %)	0.9	1.9	3.1
Group 6: 1.2_Rasagiline/LD/CD	164	137 (103 %)	57.1	47.6 (78 %)	1.0	1.5	2.8

AI	$AUC_{(0-t)}$ (ng·h/mL)	Dose normalized $AUC_{(0-t)}$* (ng·h/mL)	Cmax (ng/mL)	Dose normalized Cmax** (ng/mL)	Tmax (h)	t½ (h)	$MRT_{(po-po)}$ (h)
Group 2: 3_Rasagiline	97.3***	32.4*** (100 %)	23.3***	7.8*** (100 %)	1.2	3.3	7.0***
Group 4: 0.1_Rasagiline/LD/CD	0	n.a.	0	n.a.	n.a.	n.a.	n.a.
Group 5: 0.6_Rasagiline/LD/CD	12.2	20.3 (63 %)	3.1	5.2 (66 %)	1.5	2.3****	2.8
Group 6: 1.2_Rasagiline/LD/CD	16.7	15.6 (48 %)	4.0	3.3 (43 %)	1.4	3.3	4.1

n.a.: not applicable
* $AUC_{(0-t)}$/ dose of Rasagiline
** Cmax/ dose of Rasagiline
*** less reliable value due to high standard deviation (see Table 5, p. 606)
**** from only one animal (see Table 7, p. 606)

LD	$AUC_{(0-t)}$ (ng·h/mL)		Cmax (ng/mL)		Tmax (h)	t½ (h)	$MRT_{(po-po)}$ (h)
Group 3: 0_Rasagiline/LD/CD	17717	(100 %)	6863	(100 %)	1.0	1.1	1.9
Group 4: 0.1_Rasagiline/LD/CD	25409	(146 %)	9533	(139 %)	0.9	1.1	2.0
Group 5: 0.6_Rasagiline/LD/CD	26324	(149 %)	9537	(139 %)	0.8	1.0	2.1
Group 6: 1.2_Rasagiline/LD/CD	13078	(74 %)	4898	(70 %)	0.7	1.0	1.8

CD	$AUC_{(0-t)}$ (ng·h/mL)		Cmax (ng/mL)		Tmax (h)	t½ (h)	$MRT_{(po-po)}$ (h)
Group 3: 0_Rasagiline/LD/CD	804	(100 %)	216*	(100 %)	1.0*	3.1	2.9*
Group 4: 0.1_Rasagiline/LD/CD	898	(112 %)	233**	(108 %)	1.5	3.7	4.1
Group 5: 0.6_Rasagiline/LD/CD	1173	(146 %)	322**	(149 %)	1.1	2.5	4.7
Group 6: 1.2_Rasagiline/LD/CD	534	(66 %)	92*	(43 %)	1.3*	3.9*	7.8*

Group 6: high variability of body weights within this group
* Values less reliable since data are based on only 1-3 animals (see Tables 14 and 17, pp. 615, 618)
** values less reliable due to high standard deviations at or above 50 % of the mean (see Tables 15 and 16, pp. 616, 617)

Figure 138, from page 32 of [redacted] Project 826468

Terminal and necroscopic evaluations:C-section data (implantation sites, pre- and post-implantation loss, etc.):
There was an increase in total implant loss in groups 5 and 6, which was considered treatment related.
There were no treatment related necropsy findings.

Maternal survival and pregnancy status

Group dose in the morning dose in the afternoon		Group 1 MC 5 ml/kg MC 5 ml/kg	Group 2 BA 3 mg/kg MC 5 ml/kg	Group 3 LD/CD 40/10 LD/CD 40/10	Group 4 LD/CD+BA 0.1 LD/CD 40/10	Group 5 LD/CD+BA 0.6 LD/CD 40/10	Group 6 LD/CD+BA 1.2 LD/CD 40/10
No. of females at start	N	22	22	22	22	22	22
No. of females mated	N	22	22	22	22	22	22
Females with defined day 0 p.c.	N	22	22	22	22	22	22
Pregnant	N	20	21	21	22	20	22
- Died/sacrificed moribund	N	2	2	1	2	0	2
- Elective sacrifice	N	0	1	0	0	0	0
- Killed bec. of abortion	N	1	2	0	0	3	0
- Accidental death	N	0	0	0	0	3	0
Nonpregnant	N	2	1	1	0	2	0
- Died/sacrificed moribund	N	0	0	0	0	0	0
- Elective sacrifice	N	0	0	0	0	0	0
- Accidental death	N	0	0	0	0	0	0
Total no. of females died/ sacrificed moribund	N	3 c	5	1	2	4	2
	%	13.6	22.7	4.5	9.1	18.2	9.1
Examined at scheduled C-section	N	19	17	21	20	18	20
- Nonpregnant	N	2	1	1	0	2	0
- Pregnant	N	17	16	20	20	16	20
- with total implant loss	N	0 c	0	1	1	3	4
	%	0.0	0.0	5.0	5.0	18.8	20.0
- with viable fetuses	N	17 c	16	19	19	13	16
	%	100.0	100.0	95.0	95.0	81.3	80.0

Statistical key: c=Chi-Square

Figure 139, from page 55 of — *Project* 826468

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SUMMARY OF CESAREAN SECTION DATA

Group Dose in the morning Dose in the afternoon		Group 1 MC 5 ml/kg MC 5 ml/kg	Group 2 BA 3 mg/kg MC 5 ml/kg	Group 3 LD/CD 40/10 LD/CD 40/10	Group 4 LD/CD+BA 0.1 LD/CD 40/10	Group 5 LD/CD+BA 0.6 LD/CD 40/10	Group 6 LD/CD+BA 1.2 LD/CD 40/10
Pregnant, used for calculation	n	17	16	20	20	16	20
Early Resorptions	TOTAL	15	6	25	28	32	15
No. per animal	MEAN	0.9kd	0.4	1.3	1.4	2.0	0.8
	S.D.	1.2	0.8	1.8	1.7	1.9	1.6
% of impl. per animal	MEAN	9.2kd	6.0	13.1	22.3	23.9	10.4
	S.D.	12.7	11.6	17.5	28.7	22.4	24.2
Late Resorptions	TOTAL	6	6	4	10	5	11
No. per animal	MEAN	0.4 k	0.4	0.2	0.5	0.3	0.6
	S.D.	0.5	0.5	0.4	1.0	0.6	1.0
% of impl. per animal	MEAN	3.9 k	5.9	2.3	5.0	3.2	6.7
	S.D.	5.6	8.5	5.0	9.1	6.1	13.6
Abortion Sites	TOTAL	0	0	0	1	0	0
No. per animal	MEAN	0.0 k	0.0	0.0	0.1	0.0	0.0
	S.D.	0.0	0.0	0.0	0.2	0.0	0.0
% of impl. per animal	MEAN	0.0 k	0.0	0.0	0.4	0.0	0.0
	S.D.	0.0	0.0	0.0	1.9	0.0	0.0
Implantation Sites	TOTAL	0	0	6	0	18	20
No. per animal	MEAN	0.0 k	0.0	0.3	0.0	0.9	1.0
	S.D.	0.0	0.0	1.3	0.0	2.4	3.1
% of impl. per animal	MEAN	0.0 k	0.0	5.0	0.0	12.5	10.0
	S.D.	0.0	0.0	22.4	0.0	34.2	30.8
Postimplantation Loss	TOTAL	22	13	35	41	58	46
No. per animal	MEAN	1.3kd	0.8	1.8	2.0	3.6*	2.3
	S.D.	1.6	0.9	2.1	2.0	2.6	3.4
% impl. per animal	MEAN	13.7kd	12.5	20.4	28.5	44.4*	27.1
	S.D.	16.9	15.6	25.8	28.5	32.9	39.3
Affected Implants	TOTAL	22	13	35	41	58	47
No. per animal	MEAN	1.3kd	0.8	1.8	2.0	3.6*	2.3
	S.D.	1.6	0.9	2.1	2.0	2.6	3.3
% impl. per animal	MEAN	13.7kd	12.5	20.4	28.5	44.4*	27.6
	S.D.	16.9	15.6	25.8	28.5	32.9	38.0

Statistical key: k=Kruskal-Wallis kd=Kruskal-Wallis + Dunn * = p≤0.05
Postimplantation loss = Early/late resorptions + aborted fetuses + dead fetuses
Affected implants = Early/late resorptions + aborted fetuses + dead fetuses + malformed fetuses

Figure 140, from page 57 of — Report 826468

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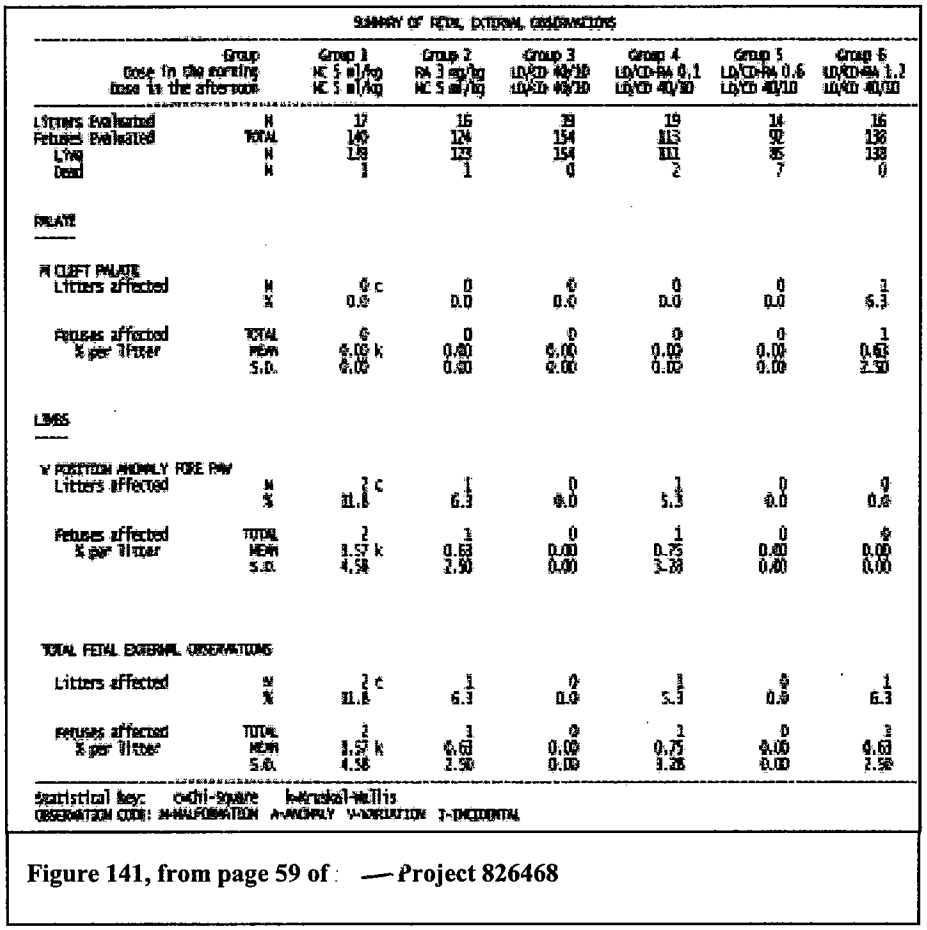
Offspring (malformations, variations, etc.):
No effects on fetal body weight
No significant increases in the incidence of external, visceral or skeletal abnormalities were observed.

Mean (SD) fetal body weights in grams

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
30.1 (4.4)	27.0 (4.1)	29.4 (2.8)	29.8 (6.2)	30.6 (5.4)	29.4 (4.0)



SUMMARY OF FETAL EXTERNAL OBSERVATIONS

Group Dose in the morning Dose in the afternoon		Group 1 HC 5 ml/kg HC 5 ml/kg	Group 2 PA 3 mg/kg HC 5 ml/kg	Group 3 LD/CD 40/10 LD/CD 40/10	Group 4 LD/CD+PA 0.1 LD/CD 40/10	Group 5 LD/CD+PA 0.6 LD/CD 40/10	Group 6 LD/CD+PA 1.2 LD/CD 40/10
Litters Evaluated	N	17	16	20	19	14	16
Fetuses Evaluated	TOTAL	149	124	154	113	92	138
Live	N	148	123	154	111	85	138
Dead	N	1	1	0	2	7	0
PALATE							
M CLEFT PALATE							
Litters affected	N	0 c	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	0.0	6.3
Fetuses affected	TOTAL	0	0	0	0	0	1
% per litter	MEAN	0.00 k	0.00	0.00	0.00	0.00	0.63
	S.D.	0.00	0.00	0.00	0.00	0.00	2.50
LIMBS							
M POSITION ANOMALY FORE PAW							
Litters affected	N	2 c	1	0	1	0	0
	%	11.8	6.3	0.0	5.3	0.0	0.0
Fetuses affected	TOTAL	2	1	0	1	0	0
% per litter	MEAN	1.57 k	0.63	0.00	0.75	0.00	0.00
	S.D.	4.58	2.50	0.00	3.28	0.00	0.00
TOTAL FETAL EXTERNAL OBSERVATIONS							
Litters affected	N	2 c	1	0	1	0	1
	%	11.8	6.3	0.0	5.3	0.0	6.3
Fetuses affected	TOTAL	2	1	0	1	0	1
% per litter	MEAN	1.57 k	0.63	0.00	0.75	0.00	0.63
	S.D.	4.58	2.50	0.00	3.28	0.00	2.50

Statistical key: c=chi-square k=Kruskal-Wallis
OBSERVATION CODE: M=MALFORMATION A=ANOMALY V=VARIATION I=INCIDENTAL

Figure 141, from page 59 of — Project 826468

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Incidences of external and visceral findings

Group	1	2	3	4	5	6
Number of Litters	17	16	20	20	16	20
Number of Fetuses	140	124	154	113	92	138
Findings (number of affected fetuses/litters)						
Forelimb, position anomaly	2/2	1/1	-	1/1	-	-
Hindlimb, position anomaly	-	-	-	-	1/1	-
Cleft palate	-	-	-	-	-	1/1
Thyroid, enlarged	-	-	1/1	-	-	-
Thymus, remnant in the neck	1/1	-	-	-	1/1	-
lung accessory lobe, absent	2/2	10/5	3/3	5/3	5/4	-
left cranial lobe, absent	-	-	-	2/1	-	-
left cranial lobe, small	-	-	-	3/2	-	-
lobes fused	3/3	-	1/1	-	-	1/1
heart enlarged				1/1		
small				1/1		
misshapen	-	-	-	-	1/1	-
malrotated				2/1	1/1	
ventricular region, misshapen (rounded)	1/1	-	-	-	1/1	-
interventricular septal defect	-	-	1/1	1/1	-	3/3
single arterial trunk, dilated	-	-	-	1/1	-	-
single arterial trunk, over-riding both ventricular chambers	-	-	-	2/1	2/2	-
left ventricular chamber enlarged	1/1	-	-	2/2	1/1	1/1
right ventricular chamber, reduced	1/1			1/1	1/1	
aortic arch, dilated	-	2/2	1/1	4/4	2/2	2/2
ascending aorta, over-riding both ventricular chambers	-	-	-	1/1	-	1/1

Figure 142, from page 60 of ' — roject 826468

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Incidences (continued)

Group	1	2	3	4	5	6
Number of Litters	17	16	20	20	16	20
Number of Fetuses	140	124	154	113	92	138
Findings (number of affected fetuses/litters)						
ductus arteriosus narrowed	-	1/1			1/1	
narrowed and non-patent				1/1		
absent	-	-	-	-	-	1/1
pulmonary trunk dilated	-	-	2/2	1/1	1/1	-
narrowed	1/1	-	-	1/1	-	-
narrowed and blind-ended	-	-	-	1/1	-	-1/1
right subclavian artery, retro-esophageal	-	1/1	3/2	1/1	2/2	-
right subclavian artery, narrowed	-	-	-	-	-	1/1
vena cava, dilated, left cranial	-	-	-	1/1	-	-
kidney and ureter, absent, right	1/1	-	1/1	-	-	1/1
pelvic dilation	-	1/1	1/1	1/1	1/1	-
adrenal, displaced, left	-	-	-	-	1/1	-
liver additional lobe	-	1/1	1/1	-	-	-
median lobe adhered to diaphragm	-	-	-	1/1	-	-
gall bladder enlarged	1/1	1/1	3/2	1/1	-	-
small	1	3	4	2	1	2
displaced	-	-	1/1	-	-	-
white fluid within abdominal cavity	-	-	-	6/1	-	-

Figure 143, from page 61 of — Project 826468

ABNORMAL FINDINGS FROM HEAD SECTIONS OF FETUSES - SUMMARY

	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
Number of litters	17		16		20		20		16		20	
Number of fetuses	140		124		154		113		92		138	
Incidences of fetuses with	N	%	N	%	N	%	N	%	N	%	N	%
Lateral ventricles, Dilation	8	5.7	4	3.2	9	5.8	8	7.1	8	8.7	5	3.6
Third ventricle, Dilation	18	12.9	6	4.8	9	5.8	11	9.7	19	20.7	10	7.2
Clotted blood between skull and cerebral hemispheres	6	4.3	3	2.4	8	5.2	5	4.4	2	2.2	4	2.9

Figure 144, from page 72 of — Project 826468

ABNORMAL FINDINGS FROM SKELETAL EXAMINATIONS OF FETUSES

Group 1: control		
Number of litters	17	
Number of fetuses	140	
Dam	Fetus	Findings
1	6	Forelimbs, bilateral: position anomaly
5	91	Cervical hemivertebra 3, right
5	93	Cervical hemivertebra 2, left Right cervical vertebral body 4 absent Right cervical vertebral arch 4 incomplete ossification
14	284	Left ribs nos. 5,6 fused Left thoracic vertebral bodies 6,7 fused Thoracic body 5, incomplete ossification
21	581	Forelimbs, bilateral: position anomaly

Group 2: RA 3 mg/kg		
Number of litters	16	
Number of fetuses	124	
Dam	Fetus	Findings
30	126	Thoracic vertebral body 11, incomplete ossification Right rib 11, absent Thoracic vertebral body 13, absent Right thoracic arch 13, absent
33	234	Tail, short Caudal vertebra 4, bipartite
37	356	Right rib 2, branched Sternebra 1, bipartite
37	360	Sternebra 1, bipartite
38	364	Thoracic hemivertebra 12, left Right rib 12, absent

Figure 145, from page 63 of [redacted] Project 826468

ABNORMAL FINDINGS FROM SKELETAL EXAMINATIONS OF FETUSES

Group 3: LD/CD 80/20 mg/kg		
Number of litters	20	
Number of fetuses	154	
Dam	Fetus	Findings
47	67	Sternebrae 3, 4 fused
50	101	Thoracic hemivertebra 3, right Left thoracic vertebral arch 4, incomplete ossification Left thoracic vertebral bodies 4, 5, fused
50	105	Sternebra 2, bipartite
54	193	Right thoracic vertebral body 7, 8, fused Right ribs 7, 8, fused at base
62	416	Sternebra 5, bipartite

Group 4: LD/CD 80/20 mg/kg + RA 0.1 mg/kg		
Number of litters	20	
Number of fetuses	113	
Dam	Fetus	Findings
67	39	Thoracic hemivertebra 12, left Right rib 12, absent
68	47	Left thoracic vertebral bodies 11, 12, fused Left thoracic vertebral arch 11, absent Left rib 11, dying
69	77	Left cervical vertebral arches 1, 2, fused Right cervical arch 5, absent Cervical vertebral bodies 4, 5, fused
70	80	Cervical hemivertebra 5, hemicentric Thoracic vertebral body 5, dumb-bell shaped Lefts ribs 5, 6 fused at base
70	81	Cervical hemivertebra 5, right
81	370	Thoracic vertebral body 5, dumb-bell shaped Right thoracic vertebral bodies 6, 7, fused Right ribs 6, 7, fused at base Right thoracic vertebral arch 7, absent
84	437	Forelimb, left: position anomaly

Figure 146, from page 64 of __ Project 826468

ABNORMAL FINDINGS FROM SKELETAL EXAMINATIONS OF FETUSES

Group 5: LD/CD 80/20 mg/kg + RA 0.6 mg/kg		
Number of litters	16	
Number of fetuses	92	
Dam	Fetus	Findings
97	200	Thoracic hemivertebra 9, left Right ribs 8, 9 centrally fused
100	278	Cervical hemivertebra 5, right Left, thoracic vertebral arch 6, absent Left rib 6, absent Left thoracic vertebral bodies 6, 7 fused Right ribs 6, 7 fused at base
105	441	Right thoracic vertebral bodies 7, 8, fused Right thoracic vertebral arches 8, 9 fused Right ribs 8, 9 fused at base
108	550	Sternebra no. 1, bipartite

Group 6: LD/CD 80/20 mg/kg + RA 1.2 mg/kg		
Number of litters	20	
Number of fetuses	138	
Dam	Fetus	Findings
123	332	Sternebrae 3, 4 fused
138	719	Left ribs 10, 11, fused at base
140	732	Sternebra 1, branched
142	740	Sternebrae 4, 5 fused
143	751	Sternebrae 2, 3, 4, and 5 fused
144	784	Left cervical vertebral body 6, absent Left ribs 1, 2, fused at base Thoracic hemivertebra 1, right Tail, short

Figure 147, from page 65 of ` — Project 826468

3.4.6.6 RASAGILINE MESYLATE (TVP-1012) STUDY FOR EFFECTS ON PRE- AND POSTNATAL DEVELOPMENT INCLUDING MATERNAL FUNCTION IN THE RAT

Key study findings:
1. 1 mg/kg caused minor maternal toxicity (decreased body weight gain) and fetotoxicity (increased pup mortality); no adverse effects were noted at 0.3 mg/kg.
2. 1 mg/kg F1 rats had slightly reduced body weights (about -5%) compared to controls, but this was not considered significant.
3. No adverse effects on pup development, learning or reproductive capacity were observed.

Study no.: — Project 828145
Location: /tox/ – Project 828145.pdf
Conducting laboratory and location: —
Date of study initiation: September 10, 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: 255400100. —

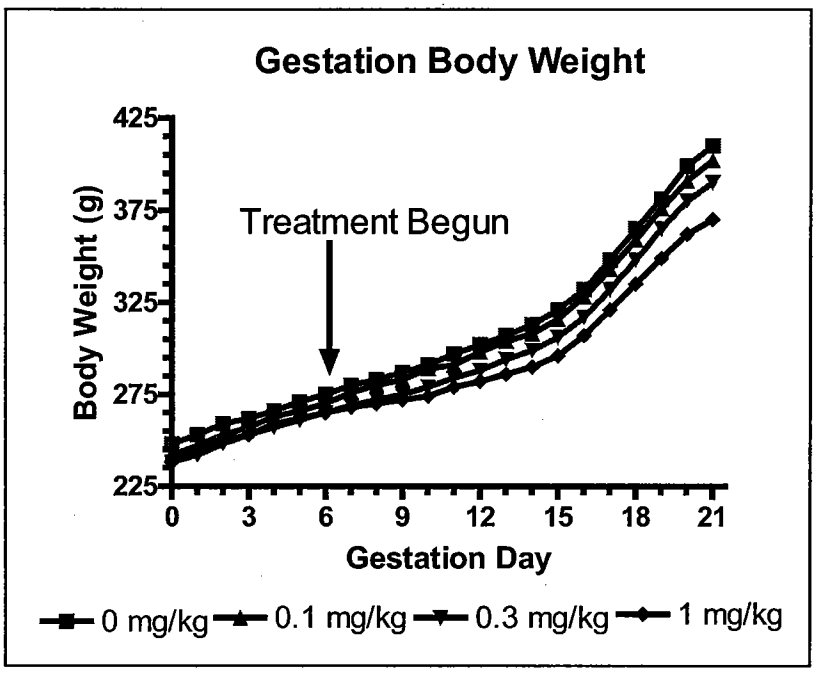
Methods

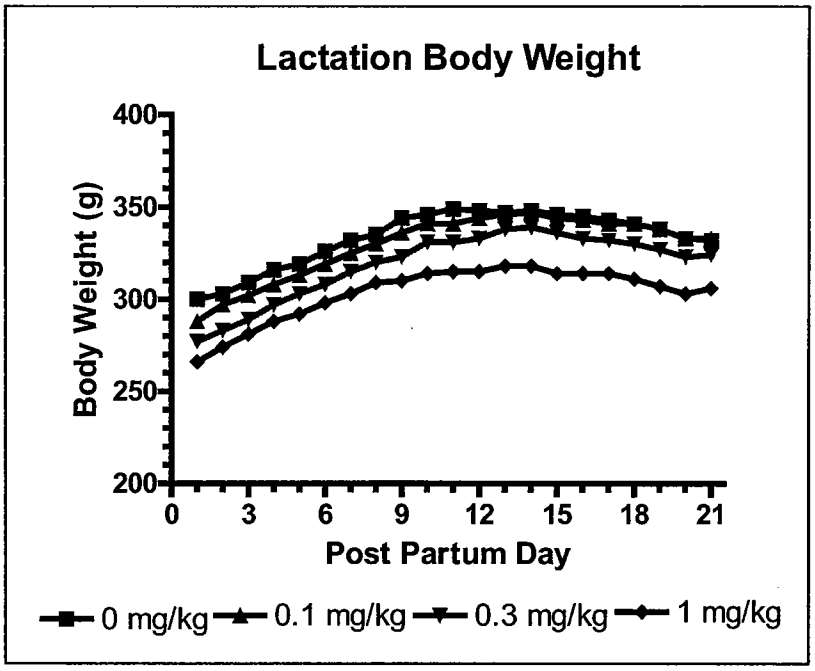
Doses: 0, 0.1, 0.3, 1 mg/kg
Species/strain: Rat Icolbm: OFA Sprague-Dawley SPF
Number/sex/group: 22 pregnant rats/group
Route, formulation, volume, and infusion rate: oral gavage
Satellite groups used for toxicokinetics: none
Study design: Dams were dosed from gestation day 6 through post partum day 20; developmental parameters and fertility were assessed in 22 pups/sex/dose in the F1 generation
Parameters and endpoints evaluated: maternal function, pup development

Results

F_0 in-life:
No deaths or clinical signs were observed in treated rats.
Body weight was about 10% lower at 1 mg/kg;
Decreased food consumption was observed at 1 mg/kg.
Increased pup mortality was observed at 1 mg/kg. An increase was also noted at 0.3 mg/kg, but this was attributed to a single litter, so the significance of this finding is uncertain.

F_0 necropsy:
No abnormalities were observed.


Gestation Body Weight
Body Weight (g)
425
375
325
275
225
Treatment Begun
0
3
6
9
12
15
18
21
Gestation Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg


Lactation Body Weight
Body Weight (g)
400
350
300
250
200
0
3
6
9
12
15
18
21
Post Partum Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg

BREEDING DATA PER GROUP
F0 GENERATION

	GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
LITTERS				
TOTAL	21	21	22	22
DURATION OF GESTATION				
MEAN (+)	21.5	21.5	21.5	21.4
ST.DEV	0.51	0.51	0.51	0.50
N	21	21	22	22
IMPLANTATIONS				
TOTAL	319	296	319	308
MEAN (+)	15.2	14.1	14.5	14.0
ST.DEV	2.40	1.84	1.99	1.90
N	21	21	22	22
POST IMPLANTATION LOSS				
% OF IMPLANTATIONS	8.5	3.4	4.1	8.4
LITTERS AFFECTED (#)	13	8	8	12
TOTAL (#)	27	10 ##	13 #	26
MEAN (+)	1.3	0.5	0.6	1.2
ST.DEV	1.45	0.68	1.01	1.40
N	21	21	22	22
DEAD PUPS AT FIRST LITTER CHECK				
LITTERS AFFECTED (#)	0	1	0	2
TOTAL	0	1	0	2
MEAN (+)	0.0	0.0	0.0	0.1
ST.DEV	0.00	0.22	0.00	0.29
N	21	21	22	22
LIVING PUPS AT FIRST LITTER CHECK				
% OF MALES / FEMALES (#)	51 / 49	53 / 47	50 / 50	51 / 49
TOTAL	292	286	306	282
MEAN (+)	13.9	13.6	13.9	13.8
ST.DEV	2.88	1.83	1.86	2.13
N	21	21	22	22
POSTNATAL LOSS DAYS 0 - 4 P.P.				
% OF LIVING PUPS	0.7	1.4	3.3	1.8
LITTERS AFFECTED (#)	2	3	1	5
TOTAL (#)	2	4	10 #	5 #
MEAN (+)	0.1	0.2	0.5	0.4
ST.DEV	0.30	0.51	2.13	1.10
N	21	21	22	22
LIVING PUPS DAY 4 P.P.				
TOTAL	290	282	296	273
MEAN (+)	13.8	13.4	13.5	13.4
ST.DEV	2.86	1.85	2.46	2.32
N	21	21	22	22
BREEDING LOSS DAYS 5 - 21 P.P.				
% OF LIVING PUPS AT DAY 4 P.P.	0.7	0.0	1.4	2.9
LITTERS AFFECTED (#)	2	0	4	8 #
TOTAL (#)	5	0	4	8 #
MEAN (+)	0.3	0.0	0.2	0.4
ST.DEV	0.80	0.00	0.59	0.49
N	21	21	22	22
LIVING PUPS DAY 21 P.P.				
% OF MALES / FEMALES (#)	51 / 49	54 / 46	51 / 49	52 / 48
TOTAL	288	282	292	265
MEAN (+)	13.7	13.4	13.3	12.0 +
ST.DEV	2.85	1.86	2.37	3.24
N	21	21	22	22

+ : Steel-test significant at 5% level
# / ## : Fisher's Exact Test significant at 5% (#) or 1% (##) level

Figure 148, from page 55 of — 'roject 828145

BREEDING DATA PER GROUP
F0 GENERATION

	GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
BIRTH INDEX (%)	91.5	96.6 ##	95.9 #	91.6
VIABILITY INDEX (%)	99.3	98.6	96.7 #	96.8 #
WEANING INDEX (%)	99.3	100.0	98.6	97.1 #

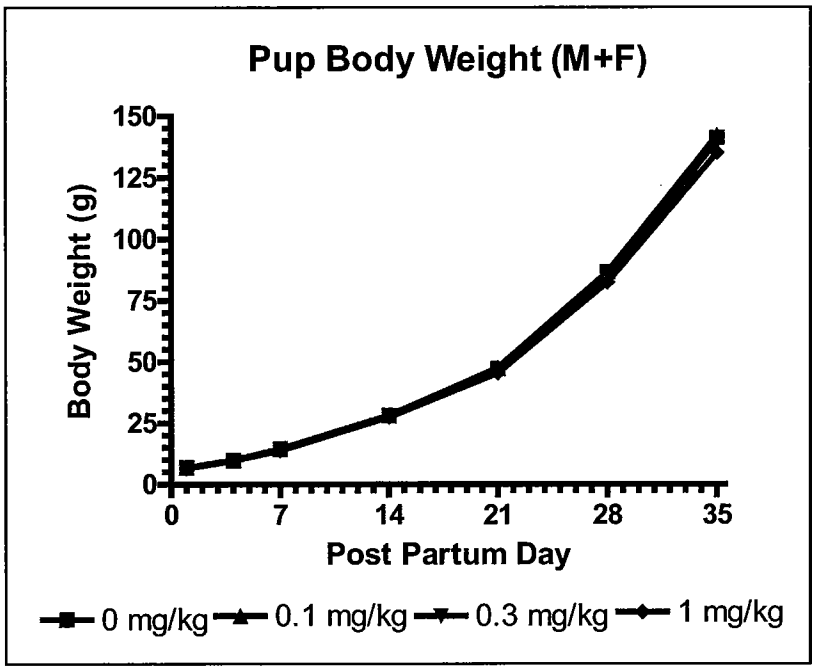
Figure 149, from page 56 of — Project 828145

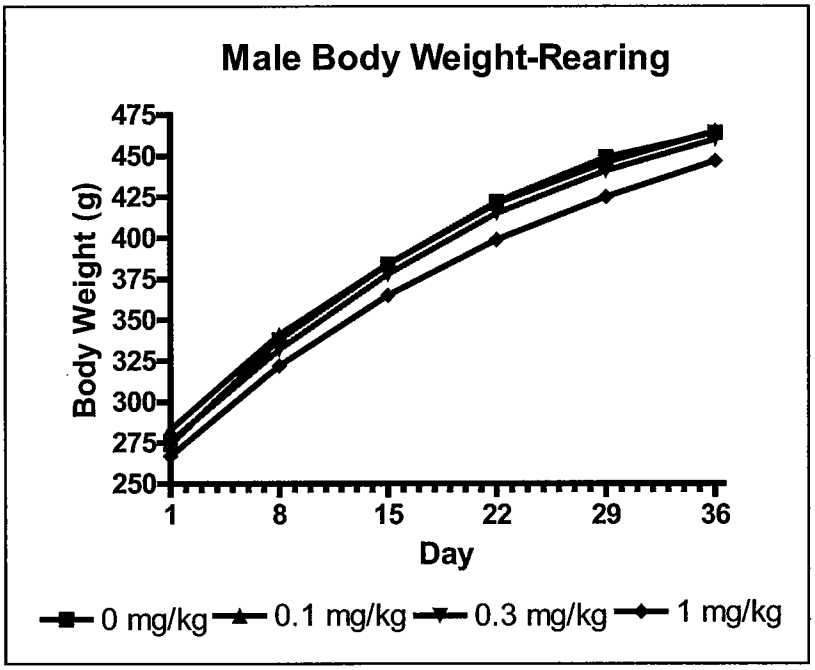
F_1 physical development:
No significant effects on body weight (1 mg/kg body weights were about 3-5% lower than controls; this was not considered significant).
No significant effects on physical development.
No significant clinical signs were observed in developing pups.

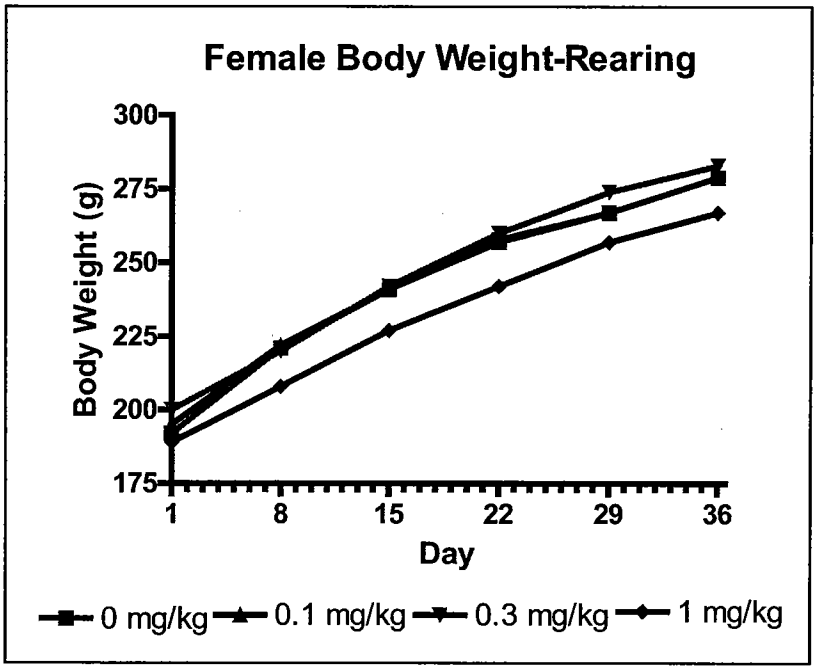
DEVELOPMENTAL INDICES PER GROUP (DAYS P.P.)
F1 PUPS

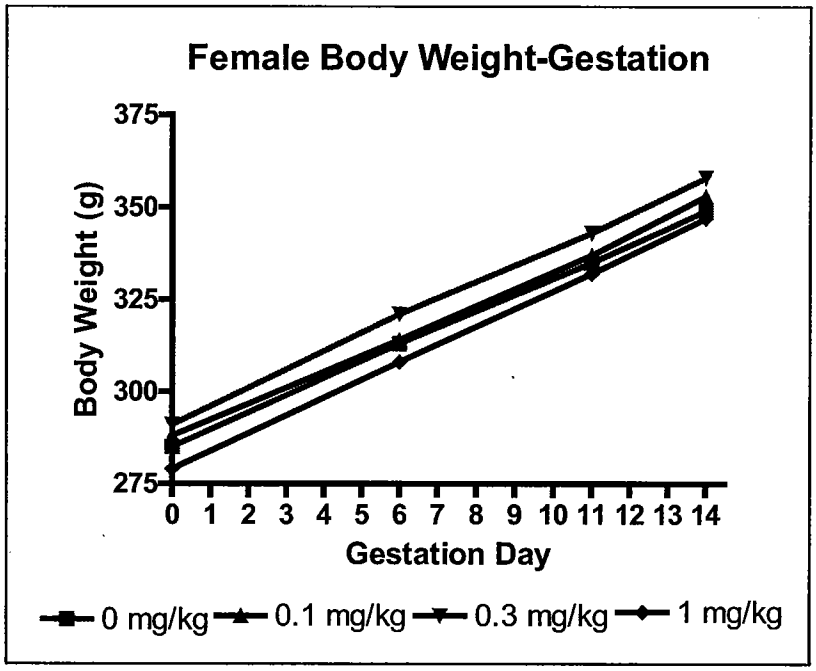
		GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
Pinna unfolding	Mean	3.0	3.1	3.2	3.2
	St.dev.	0.58	0.66	0.41	0.59
	N	21	21	22	22
Incisor eruption	Mean	7.0	7.2	7.4 +	7.2
	St.dev.	0.40	0.29	0.49	0.20
	N	21	21	22	22
Onset of coat development	Mean	8.9	8.5	8.5	8.6
	St.dev.	0.73	0.60	0.67	0.66
	N	21	21	22	22
Opening of eye	Mean	14.6	14.5	14.7	14.6
	St.dev.	0.58	0.56	0.88	0.65
	N	21	21	22	22
Descensus of testes	Mean	23.8	24.2	24.1	23.8
	St.dev.	0.77	0.71	0.61	0.91
	N	21	21	22	22
Opening of prepuce	Mean	25.7	26.0	26.0	25.8
	St.dev.	0.45	0.62	0.61	0.80
	N	21	21	22	22
Opening of vagina	Mean	32.2	32.1	31.9	31.7
	St.dev.	0.73	0.92	1.13	0.66
	N	21	21	22	22

Figure 150, from page 78 of — Project 828145


Pup Body Weight (M+F)
Body Weight (g)
150
125
100
75
50
25
0
0
7
14
21
28
35
Post Partum Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg


Male Body Weight-Rearing
Body Weight (g)
475
450
425
400
375
350
325
300
275
250
1
8
15
22
29
36
Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg


Female Body Weight-Rearing
Body Weight (g)
300
275
250
225
200
175
1
8
15
22
29
36
Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg


Female Body Weight-Gestation
Body Weight (g)
375
350
325
300
275
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Gestation Day
0 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg

F_1 behavioral evaluation:
No significant effects on learning.

BEHAVIOURAL TESTS
F1 PUPS

TEST	PERFORMED ON DAYS P.P.	SCORE	MEANING
Righting reflex	14 ± 1	0	negative
		1	positive
Photo-phobotaxis	21 ± 1	0	never positive
		1	once positive
		2	twice positive
Pupillary reflex	21 ± 1	0	negative
		1	positive
Hearing ability	21 ± 1	0	negative
		1	positive
Palmar grasp ability	16 ± 1	0	negative
		1	positive
Activity Test	21 ± 1	0	no activity
		1	explorat. behaviour
		2	rearing against wall
		3	trying to escape
Cliff avoidance	21 ± 1	0	negative
		1	positive
Negative geotaxis	21 ± 1	0	negative
		1	positive
Water maze 1. learning	35 ± 1	0	no learning
		1	learning
Water maze 2. learning	35 ± 1	0	no learning
		1	learning
Water maze 3. learning	35 ± 1	0	no learning
		1	learning
Water maze 4. learning	35 ± 1	0	no learning
		1	learning
Water maze 5. learning	35 ± 1	0	no learning
		1	learning
Water maze 6. learning	35 ± 1	0	no learning
		1	learning
Water maze memory	43 ± 1	0	no memory
		1	memory
Water maze 1. relearning	43 ± 1	0	No learning
		1	Learning
Water maze 2. relearning	43 ± 1	0	No learning
		1	Learning
Water maze 3. relearning	43 ± 1	0	No learning
		1	Learning
Water maze 4. relearning	43 ± 1	0	No learning
		1	Learning
Water maze 5. relearning	43 ± 1	0	No learning
		1	Learning
Water maze 6. relearning	43 ± 1	0	No learning
		1	Learning

Figure 151, from page 83 of — Project 828145

BEHAVIOURAL TESTS PER GROUP
F1 PUPS

		GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
Righting reflex	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Photo-phobotaxis	Mean (+)	72 %	48 %	70 %	72 %
	N	21	21	22	22
Pupillary reflex	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Hearing ability	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Palmar grasp ability	Mean (%)	100 %	100 %	100 %	100 %
	N	20	21	22	22
Activity Test	Mean (+)	2.0	2.0	2.0	2.0
	N	21	21	22	22
Cliff avoidance	Mean (%)	99 %	97 %	98 %	99 %
	N	21	21	22	22
Negative geotaxis	Mean (%)	96 %	95 %	89 % **	97 %
	N	21	21	22	22
Water maze 1. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 2. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 3. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 4. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 5. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 6. learning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze memory	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 1. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 2. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 3. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 4. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 5. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22
Water maze 6. relearning	Mean (%)	100 %	100 %	100 %	100 %
	N	21	21	22	22

Figure 152, from page 84 of — Project 828145

F_1 reproduction:
No effects were observed on time to mating, fertility or embryo development

FERTILITY
F1 GENERATION

FEMALES SCHEDULED FOR CAESAREAN SECTION

	GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
Percentage mating	100.0	100.0	100.0	100.0
Fertility index (%)	90.9	95.5	90.9	86.4
Conception rate (%)	90.9	95.5	90.9	86.4
Gestation index (%) (Caesarean section)	95.0	100.0	100.0	94.7

Figure 153, from page 120 of — Project 828145

APPEARS THIS WAY
ON ORIGINAL

REPRODUCTION DATA SUMMARY
F1 GENERATION

	GROUP 1 0 MG/KG	GROUP 2 0.1 MG/KG	GROUP 3 0.3 MG/KG	GROUP 4 1.0 MG/KG
NUMBER OF DAMS	19	21	20	18
CORPORA LUTEA	323	367	351	315
MEAN (+)	17.0	16.5	17.6	17.5
ST.DEV.	3.1	2.0	1.9	1.9
PRE-IMPLANTATION LOSS	11	4	3	9
% OF CORP. LUTEA (#)	3.4	1.1 *	0.9 *	2.9
MEAN (+)	0.6	0.2	0.2	0.5
ST.DEV.	1.2	0.6	0.4	1.0
NUMBER OF DAMS AFFECTED	4	2	3	4
IMPLANTATION SITES	312	363	348	306
% OF CORP. LUTEA (#)	96.6	98.9 *	99.1 *	97.1
MEAN (+)	16.4	16.3	17.4	17.0
ST.DEV.	3.1	2.1	1.8	2.0
POST-IMPLANTATION LOSS	20	22	17	18
% OF IMPL. SITES (#)	6.4	6.4	4.9	5.9
MEAN (+)	1.1	1.0	0.9	1.0
ST.DEV.	1.1	1.0	0.7	1.0
NUMBER OF DAMS AFFECTED	13	14	13	12
IMPLANTATION SITE SCARS	0	0	0	0
EMBRYONIC/FETAL DEATHS TOTAL	20	22	17	18
EMBRYONIC RESORPTIONS	18	18	15	16
% OF IMPL. SITES (#)	5.8	5.2	4.3	5.2
MEAN (+)	0.9	0.9	0.8	0.9
ST.DEV.	0.8	1.0	0.8	1.0
NUMBER OF DAMS AFFECTED	13	12	11	11
FETAL RESORPTIONS	2	4	2	2
% OF IMPL. SITES (#)	0.6	1.2	0.6	0.7
MEAN (+)	0.1	0.2	0.1	0.1
ST.DEV.	0.3	0.5	0.3	0.3
NUMBER OF DAMS AFFECTED	2	3	2	2
FETUSES				
TOTAL FETUSES	292	321	331	288
% OF IMPL. SITES (#)	93.6	93.6	95.1	94.1
MEAN (+)	15.4	15.3	16.6	16.0
ST.DEV.	1.3	2.1	2.0	1.9
LIVE FETUSES	292	321	331	288
DEAD FETUSES	0	0	0	0

Figure 154, from page 121 of — Report 828145

F_2 findings:
None

3.4.7 Local tolerance

No Studies Submitted

3.4.8 Special toxicology studies

No studies submitted.

3.5 OVERALL CONCLUSIONS AND RECOMMENDATIONS

3.5.1 Introduction

Parkinson's disease is a neurodegenerative disease characterized by bradykinesia, muscular rigidity, resting tremors, and postural instability. If left untreated, it will progress to a rigid akinetic state in which the patient is incapable of taking care of him/herself. Pathologically, Parkinson's disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra resulting in decreased dopaminergic tone. Since the cause of this loss is unknown at present, current therapy for Parkinson's disease utilizes substances that increase dopaminergic tone (e.g., ropinerole, pramipexole) or increase the amount of dopamine available at the receptor site (e.g. levodopa, COMT inhibitors, MAO-B inhibitors). Despite the use of these drugs, patients may still experience "off" episodes in which their muscle movement is slow or frozen. These off episodes are thought to be the result of deficient dopaminergic tone.

In the brain, there are three primary methods of terminating dopamine's action. Dopamine can be taken up into the presynaptic terminal. It may be methylated to 3-methoxytyramine by catechol-O-methyl transferase (COMT). Finally, it may undergo oxidative deamination to 3,4-dihydroxyphenylacetic acid (DOPAC) by MAO. In humans, MAO-B is responsible for this conversion, but in rats, MAO-A is the primary enzyme. Both 3-methyoxytyramine and DOPAC can be further metabolized to 3-methyoxy-4-hydroxy-phenylacetic acid (HVA) by MAO and COMT, respectively. Drugs that inhibit either COMT or MAO would be expected to increase the amount of dopamine available in the brain for interacting with the dopamine receptor.

Rasagiline is a MAO-B inhibitor which is proposed for the treatment of Parkinson's disease. It is structurally similar to selegiline (Eldepryl), another MAO-B inhibitor which is approved for the treatment of Parkinson's disease.

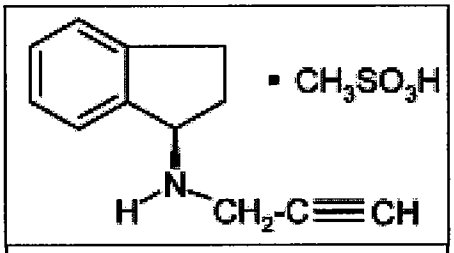


Figure 155, Rasagiline (Agilect)

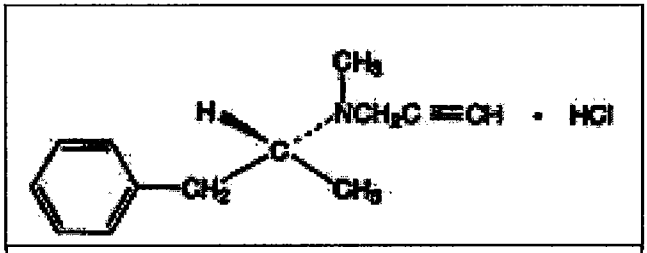


Figure 156, Selegiline (Eldepryl)

3.5.2 Pharmacology of Rasagiline

Pharmacology studies examine whether a drug has desirable characteristics which would make it useful in the clinic. First, the drug needs to interact with an appropriate target, e.g., by inhibiting a target enzyme. Second, the drug should inhibit the target enzyme in the target organ. Third, the drug should be relatively specific for the target enzyme. Fourth, the drug may be assessed for secondary effects which may contribute to its pharmacological action. Finally, drugs are often examined for activity in animal models of the disease of interest. For Parkinson's disease, two common models involve treating animals with MPTP or 6-hydroxy-DOPA (6-OH-DOPA). Both of these drugs preferentially injure dopaminergic neurons resulting in symptoms similar to Parkinson's disease.

Rasagiline is a propargylamine based drug for the treatment of Parkinson's disease. It has a single chiral center. The R-enantiomer is the active moiety with a IC_{50} of 2.5 nM for rat brain MAO-B compared to an IC_{50} of 17,000 nM for the S-enantiomer (TVP-102). Rasagiline also inhibits the human cortex MAO-B, although an IC_{50} could not be calculated, it would appear to be between 1 and 10 nm. Rasagiline has a 29-fold greater specificity for MAO-B over MAO-A in vitro (2.5 nM versus 73 nM using rat brain homogenate). In human cortex homogenate, rasagiline also has a preference for MAO-B over MAO-A (IC50 would be between 100 and 1000 nM). This is a desirable characteristic since inhibition of MAO-A is associated with the "cheese effect", a pressor reaction to dietary tyramine that results in increased blood pressure. Studies in rats suggest that a single dose of rasagiline (1 mg/kg ip) could inhibit MAO-B for up to 72 hours (about 70% inhibition at 72 hours, the last timepoint assessed) (see page 7). The parent compound is responsible for MAO inhibition in vivo since the primary metabolite, AI, does not inhibit MAO-B in vitro (IC50 = 20,000 nM, see page 36). Rasagiline has been examined for the ability to interact with a panel of receptors (including dopamine receptors) and enzymes tested (see page 26). Rasagline did not interact to any significant extent with any of the receptors or enzymes. Among the targets examined were the dopamine receptors (D1-D4), dopamine transporter, tyrosine hydroxylase (responsible for the conversion of tyrosine to L-DOPA). Aromatic amino acid decarboxylase (responsible for the conversion L-DOPA to dopamine) was not examined in this study.

Rasagiline is also an effective inhibitor of MAO-B in vivo. The IC_{50} for inhibiting rat brain MAO-B was 0.17 and 0.07 mg/kg by oral and intraperitoneal administration, respectively. In contrast, the IC_{50} for inhibiting rat brain MAO-A was >10 and 1.2 mg/kg by oral and intraperitoneal administration. This suggests that rasagiline is relatively specific for MAO-B in vivo (see page 7). Similarly in mice, an acute dose (0.06 mg/kg sc) that caused near complete inhibition of brain MAO-B activity had virtually no effect on brain MAO-A activity (see page 16). However, the goal of treatment with rasagiline is to decrease MAO-B activity by more than 50%. As the dose is increased, there is potential for inhibition of the non-target MAO-A. For instance, in rats chronically administered 0.3 and 0.5 mg/kg (males and females, respectively), brain MAO-A activity was inhibited by 79% and 75%, respectively (see page 11). It was also noted that the low doses in the mouse and dog toxicology studies resulted in inhibition of MAO-A as well as near complete inhibition of MAO-B (see pages 14, 17).

Studies on rasagiline have used both the hydrochloride salt (TVP-101) and the mesylate salt (TVP-1012). The sponsor has compared the in vitro and in vivo

pharmacology of the two salt forms. The two salts (compared on a free base basis) are virtually identical in their pharmacological activity in vitro and in vivo (see pages 9,10).

The sponsor has done minimal work in evaluating the efficacy of rasagiline in animal models of Parkinson's disease. In these studies, rasagiline was administered to mice one hour prior to MPTP injection. MPTP treatment destroyed dopaminergic neurons as indicated by decreases in striatal dopamine. Rasagiline pretreatment prevented the dopamine depletion in MPTP treated mice (see pages 22, 22 and 23). This inhibition was observed at doses (as low as 0.2 mg/kg) that selectively inhibited MAO-B. However, this reviewer does not regard this study as being useful in the determining the potential efficacy of rasagiline in Parkinson's disease. MPTP must be activated to the neurotoxin MPP+ via MAO-B. Since rasagiline inhibits MAO-B, it prevented the formation of the toxic intermediate. Thus, the effectiveness of rasagiline is specific to this toxin and has doubtful relevance for idiopathic Parkinsons disease. It is noteworthy that when the rasagiline (5 or 10 mg/kg) was given to mice one to four hours after MPTP treatment, rasagiline was ineffective in preventing dopamine depletion in the striatum (see page 23). It is concluded that rasagiline has not demonstrated activity in animal models of Parkinson's disease which would be considered relevant for humans. This is not important, however, since rasagiline has been shown to have pharmacological activity (MAO-B inhibition) which has been shown to be relevant to the treatment of Parkinson's disease.

In conclusion, the sponsor has demonstrated that rasagiline is a relatively specific inhibitor of MAO-B over MAO-A. Inhibition of MAO-B is a relevant pharmacologic activity for a potential Parkinson's disease drug. The activity resides in the parent compound and is specific for the R-enantiomer. Both the mesylate salt and the hydrochloride salts are effective in vivo and in vitro. Rasagiline is capable of crossing the blood-brain barrier and inhibiting MAO-B. The inhibition is long lasting (inhibition is observed out to 72 hours following acute treatment). There is also potential for rasagiline to inhibit MAO-A following chronic treatment.

3.5.3 Pharmacokinetics of Rasagiline

The purpose of the pharmacokinetic evaluation is to determine whether the pharmacokinetics of the drug substance is similar in humans and the nonclinical species. If humans make a metabolite that is not made in preclinical species, then the preclinical studies may not identify all the potential toxic effects of a compound. Likewise, if an animal makes a metabolite that is not present in humans, then it may predict toxicities that may not occur in humans. Concurrence in the formation of metabolites offers assurances that the nonclinical studies are valid models for human exposures.

The pharmacokinetics of rasagiline has been examined in mice, rats, and dogs. Comparative studies of the oral pharmacokinetics of the mesylate and hydrochloride salts of rasagiline have been conducted in rats (see page 41) and dogs (see page 43). The two salts have very similar pharmacokinetic properties as indicated by similar Cmax, AUC, and Tmax values following equal doses of the free base. In addition, primary metabolite AI had similar pharmacokinetic properties as indicated by similar Cmax, AUC and Tmax values following administration of the two salt forms. For the purposes of this discussion, no distinction will be made between the two salt forms.

Although comparative studies between oral and IV exposures have not been conducted, rasagiline has adequate oral bioavailability. Mass balance studies in mice (see page 37), rats (see page 44) and dogs (see page 46) using radiolabelled rasagiline found the 80-90% of orally administered radiolabel was excreted in the urine within 6 to 24 hours. In addition, the pharmacology studies suggest that oral doses of less than 1 mg/kg are effective in inhibiting brain MAO-B in rats.

Following absorption from the gut, rasagiline is rapidly distributed through the body into the tissues. Maximum concentrations of radiolabel in rats were observed 15 minutes following administration, primarily in the skeletal muscle, liver and skin (see page 44). The in vitro protein binding of rasagiline has been examined in human, mouse, rat, and dog plasma proteins (see page 45). About 90-93% of rasagiline was bound to human plasma proteins at protein concentrations between 1 and 100 ug/ml; in contrast, binding in mouse, rat, and dog plasma proteins were 73%, 78-79% and 83-86%, respectively.

Rasagiline is rapidly metabolized. Only 11% of circulating drug related material was chromatographically identical to parent following 0.45 mg/kg po in the rat. Similarly in dogs, only 4.8% and 1.2% of circulating radiolabel was parent compound 1 and 2 hours, respectively, after a dose of 1 mg/kg po (see page 46). Corresponding values of the metabolite AI were 4.7% and 4.6%. The remaining 90% of circulating radiolabel was unidentified. The sponsor has not characterized circulating metabolite levels in mice, rats or dogs. Most of the available information on in vivo metabolism is derived from analysis of urinary metabolites. In rats, the primary urinary metabolites are 3-OH-AI, AI and 3-OH-AAI in descending order (see page 47, 48). In dogs, the main urinary metabolite identified was 3-OH-PAI followed by 3-OH-AI and AI (see page 46). In all species, at least nine distinct urinary metabolites were identified. Studies using hepatic microsomal preparations have been performed using mouse, rat, dog, and human samples (see page 50). AI was a major component in all species tested; 3-OH-PAI was identified as a major metabolite in rat and dog preparations, but was a minor component in human and mouse microsomal preparations. The sponsor has proposed a metabolic pathway for rats; in addition, the sponsor has prepared a semi-quantitative comparison of

urinary metabolites in mice, rats, dogs and humans (see below). It is noted that a major component of this table is unidentified polar metabolites. In addition, these are pooled urinary metabolite values and do not reflect circulating metabolite levels. The sponsor will need to identify the circulating metabolites in mice, rats, and dogs prior to approval of this application.

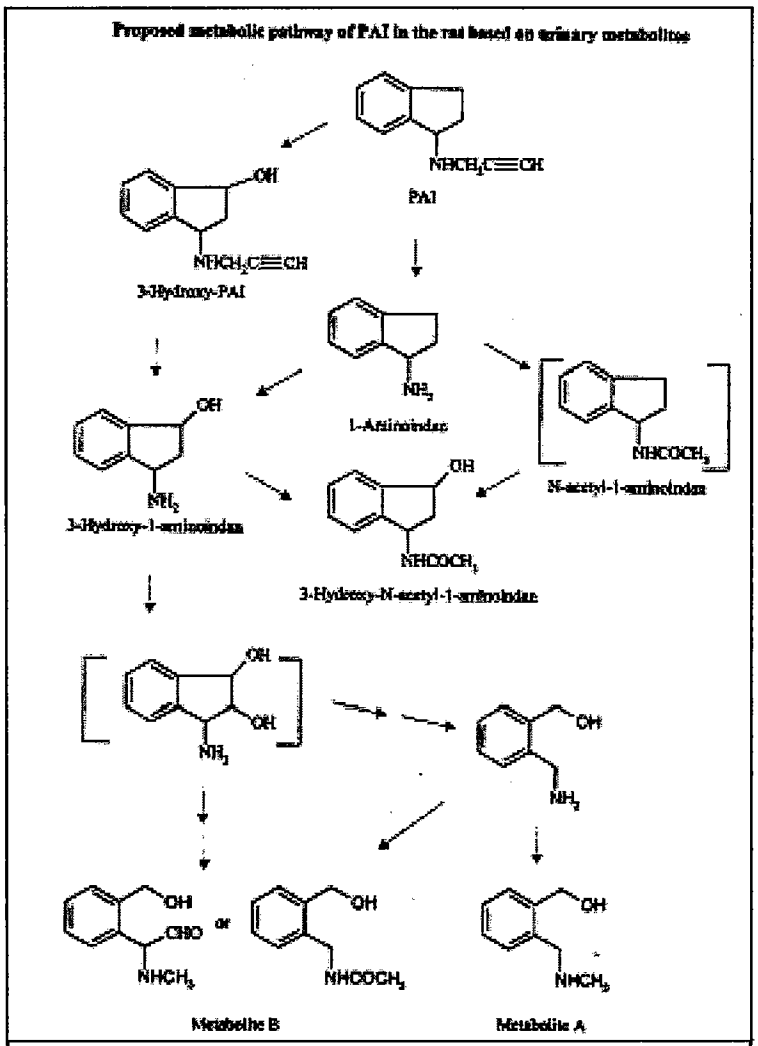


Figure 157, from page 22 of Report TVA 12498688

Table 2. Semi-Quantitative Comparison of Urine Metabolites in Different Species (% of administered dose in urine collected 0 – 48 hours post dose)

Species	Mice	Rat	Dog	Human
Study Number	SB-2001-039	SB-2001-001	SB-2002-007[3]	SB-2001-018[3]
		Metabolite		
Polar	6.2 - 32	37 - 43	69	21
3- OH-AI	4.7 – 7.0	14 – 16	2.8	2.0
3-keto-AI	0.9 -1.7	1.8 – 3.2	1.1	
AI	7.7 – 18.5	7.5 – 11.1	2.5	21
3-OH-PAI	< 1	< 1	<1	
3-keto PAI		< 1		
PAI	1.7 - 3.5	1.0 – 3.4	<1	0.7 – 1.4
Indanone		<1	Traces	
		Phase II metabolites in different species		
Conjugated PAI[2]	1.2 – 3.3[3]	0.4 – 1.0	<0.6	5.5[4]
Conjugated AI[2]		0.7 – 1.1	0.6	7[4]
Conjugated 3-OH-PAI[2]	2 – 3.5[3]	0.3 – 2.1	8.0	14[4]
3-OH- AAI		7.9 – 9.2		1.9 – 2.3[4]
3-keto-AAI		0.7 – 1.4		<2[4]

Figure 158, from page 19 of Sponsor Nonclinical Overview

In summary, rasagiline is rapidly absorbed following oral administration. It is extensively metabolized, but the identity of the circulating metabolites is (are) have not been determined. In toxicokinetic studies associated with the toxicology studies, the sponsor has monitored parent and AI plasma concentrations. However, data in the dog suggest that these two compounds account for less than 10% of circulating radioactivity in mass balance studies. Rasagiline is excreted via urine.

3.5.4 Toxicology of Rasagiline

For the purpose of examining the toxicity, it is useful to have some parameter to compare the doses among species. Plasma levels of the drug expressed as the maximum concentration (Cmax) and the average drug concentration over a specified period (AUC) are useful parameters for comparing doses. At the recommended clinical dose of 1 mg/day, the Cmax is 8.5 ng/ml while the AUC(0-inf) is 13.5 ng-hr/ml.

3.5.4.1 Safety Pharmacology

The purpose of safety pharmacology studies is to detect forms of toxicity that can not be assessed via traditional toxicology studies. Rasagiline has been evaluated for effects on the central nervous system, cardiovascular system, and the renal system. The renal safety pharmacology study will be discussed in the section on rasagiline's interactions with sinemet (see page 213). No studies were submitted on the potential for rasagiline to affect the respiratory or gastro-intestinal systems.

The potential effects of rasagiline on the central nervous system were examined in two studies. Rasagiline had no effect on rat behavior at doses up to 2 mg/kg in the Irwin test (see page 29). In another test, rasagiline was administered to mice at doses of 3, 10, 30 or 100 mg/kg ip and locomotor activity was followed for 60 minutes (see page 29). A dose dependent decrease in locomotor activity was observed starting at 10 mg/kg. Rasagiline also did not potentiate cocaine (20 mg/kg ip) induced hyperactivity in mice. It is concluded that rasagiline had no adverse effects in neurological safety pharmacology studies.

The potential effects of rasagiline on the cardiovascular system were examined in two safety pharmacology studies as well as a component of the dog toxicity studies. In a safety pharmacology study in the dog, 3 mg/kg rasagiline PO had no effect on ECG parameters or blood pressure for up to 24 hours (see page 31). In another study, rats were administered 1 or 5 mg/kg IV and monitored for 16 hours (see page 31). At 5 mg/kg, rasagiline decreased the heart rate by about 15%. This dose had no effect on blood pressure and ECG parameters were not examined in this study. No effects were observed at 1 mg/kg rasagiline or with AI at 5 mg/kg IV. The sponsor has not conducted a HERG assay.

It is concluded that rasagiline did not have any adverse effects in the safety pharmacology studies submitted in this application.

3.5.4.2 Toxicology

The acute toxicity of the hydrochloride and mesylate salts of rasagiline was examined in rats (see page 55). When calculated as free base, the LD50's of the two salt forms were similar (227 mg/kg for the hydrochloride versus 256 mg/kg for the mesylate salt for the two sexes combined). Similar clinical signs (lethargy, decreased respiratory rate) were observed in rats treated with the two salt forms. Mortality was observed at doses as low as 133 mg/kg.

In the 26 week rat study (see page 57), rats were administered 0, 0.85, 5.1 or 17 mg/kg by oral gavage. The primary adverse effect observed was decreased body weight (defined as final body weight $\leq$90% of control values) starting at 5.1 mg/kg in males and 17 mg/kg in females. The primary clinical signs were salivation at 5.1 mg/kg and above and behavioral alterations (subdued, aggressive) at 17 mg/kg. No adverse effects were

noted on hematological, clinical chemistry, urinalysis or ophthalmoscopy examinations. Alterations were noted in the in liver (increased adjusted liver weight and centrilobular hypertrophy) at 17 mg/kg, but these alterations were considered adaptive changes rather than adverse effects. Similarly, the thyroid follicular cell hypertrophy observed at 17 mg/kg was considered secondary to the liver hypertrophy. It was concluded that the NOAEL in this study was 0.85 mg/kg in males and 5.1 mg/kg in females. AUC levels were not calculated in this study. However, the 0.25 hour rasagiline concentrations may be used as a Cmax. The Cmax at the NOAEL's in males and females were 80 and 351 ng/ml, respectively. These values are 9.5 and 41 times the human Cmax values, respectively.

The sponsor has also conducted 4 and 13 week studies in rats. These studies were not reviewed because the high dose used in those studies (17 mg/kg for both studies) was the same as was used in the 26 week study. A cursory review of these studies did not suggest that these had any independent significance. Therefore, these studies were not reviewed in this report.

In a 13 week mouse study, mice were administered 0, 5, 15, 45, 60 or 100 mg/kg (see page 75). Decreased body weight gains were observed at 45 mg/kg and above, but the differences were not consistently dose dependent in either sex. Liver hypertrophy was observed at 15 mg/kg and above in males and 60 mg/kg and above in females. This is generally considered an adaptive change. Lymphoid necrosis of the thymus was observed in females at 100 mg/kg. It is concluded that the NOAEL's in males and females were 15 and 45 mg/kg, respectively. Toxicokinetic monitoring was conducted only on mice administered 5, 45 or 60 mg/kg. At 45 mg/kg, the Cmax values were 892 and 1,913 ng/ml in male and female mice, respectively. These values are 105 and 225 times the human Cmax. At 45 mg/kg, the AUC(0-24) values were 3934 and 3800 ng-hr/ml in male and female mice respectively. These values are 291 and 281 times the human AUC values.

In a maximum tolerated dose study (see page 56), both dogs administered 84 mg/kg as a single oral dose died within two to three days. Clinical signs included vomiting, diarrhea, decreased food consumption and blood in the mouth and feces. The only significant clinical sign noted at 42 mg/kg was diarrhea.

In the 52 week dog study (see page 81), dogs were administered rasagiline at doses of 0, 0.85, 5.1 or 21 mg/kg/day in gelatine capsules. One 21 mg/kg dog was found dead at week 51; this dog had an isolated convulsion during week 33 but no other clinical signs were noted. The high dose dogs had lower body weight gains than in the other groups. There were no treatment related clinical signs noted. No effects were observed on ophthalmologic evaluation. Rasagiline had no effect on the heart rate or ECG waveforms, but quantitative measurement of ECG parameters (eg, QT interval) were not calculated. High dose dogs had higher cholesterol and triglyceride levels, but no other alterations were noted in hematological, clinical chemistry or urinalysis tests. No effects were noted on organ weight, gross pathology or histopathology. The NOEL in this study is 5.1 mg/kg based on decreased weight and mortality (in a single dog) at 21 mg/kg. AUC levels were not calculated in this study. However, the 0.75 hour rasagiline concentrations may be used as a Cmax. The Cmax at the NOAEL's in males and females were 166 and 184 ng/ml, respectively. These values are 20 and 22 times the human Cmax values, respectively.

The sponsor has also conducted 4 and 13 week studies in dogs. These studies were not reviewed because the high dose used in those studies (17 mg/kg for both studies) was lower than the dose used in the 52 week study (21 mg/kg). A cursory review of these studies did not suggest that these had any independent significance. Therefore, these studies were not reviewed in this report.

In summary, rasagiline has been tested at doses up to 100 mg/kg for 13 weeks in mice, 17 mg/kg for 26 weeks in rats and 21 mg/kg for 52 weeks in dogs. Adverse effects were generally limited to body weight changes. No specific target organ toxicities were identified in these studies. The plasma levels of rasagiline in the toxicity studies were higher than the plasma levels observed in the clinic.

3.5.4.3 GENOTOXICITY

Rasagiline was examined in for mutagenic potential in three bacterial mutations assays (Ames assays) (see pages 93, 95, 97). Two of the studies used an appropriate range of Samonella typhimurium strains. However, one of the studies did not have a AT point mutation strain (such as TA102 or E. coli WP2). All three of the studies used concentrations up to the limit dose for the assay (5000 ug/plate) and had appropriate positive and negative controls. Rasagiline did not increase the rate of mutations in any of the assays.

Rasagiline was examined for mutagenic potential in a series of three in vitro chromosomal aberration studies in human peripheral lymphocytes and in an in vitro mouse lymphoma assay with and without glutathione. The chromosomal aberration studies used both the mesylate salt and the hydrochloride salt. Both salts caused an increase in the incidence of chromatid deletions in the presence of metabolic activation. The hydrochloride salt caused chromatid deletions at 1168 (the lowest dose evaluated), 1558 and 2077 ug/ml following treatment in the presence of metabolic activation for three hours (see page 106). The aberrations occurred at doses that caused a 53-57% decrease in mitotic index (MI), suggesting the aberrations were not due to excessive cytotoxicity. The mesylate salt caused a dose dependent increase in chromatid deletions between 63.5 and 2670 ug/ml (see page 99). The aberrations occurred at doses that caused a 27-54% decrease in MI, suggesting the aberrations were not due to excessive cytotoxicity. In the other chromosomal aberration study, rasagiline was positive only at the highest dose tested (2673 ug/ml) in the presence of metabolic activation at 17 hours post exposure, but not at 41 hours post exposure (see page 102). The sponsor suggests that the difference may be due to the presence of gentamycin in the culture media of the first two studies, but not in the last study. However, there were multiple differences in the conduct of the study (fetal bovine serum concentration, S9 concentration). In addition, the sponsor did not conduct a direct comparison of the genotoxicity of rasagiline in the presence and absence of gentamycin. The sponsor has proposed to add language to label stating the

This reviewer considers this to be speculative and inappropriate for inclusion in the label. The sponsor also examined the potential effects of glutathione on rasagilne genotoxicity in this study. However, the studies conducted in the presence of glutathione appear to be inadequate. In the 46 hour sampling time, the mitotic index for the high rasagiline concentration was about 70% of control values. For doses to be considered adequate in these assays, the high dose should cause at least a 50% decrease

in mitotic index (ICH guideline S2A). In addition, a positive control was not used in the presence of glutathione. This reviewer regards this section of the study as being inadequate.

Rasagiline was positive in the mouse lymphoma assay in the presence and absence of metabolic activation (see page 109). The increase was increased only at the highest dose (1000 ug/ml) in the presence of metabolic activation. In the presence of metabolic activation, an increase was observed at 2.5 ug/ml (non-significant) and 5.0 ug/ml (significant, highest dose). An increase was also observed at the lowest dose in the presence of metabolic activation (0.25 ug/ml), but not at two intermediate doses (0.5 and 1 ug/ml). In an additional study, rasagiline tested in the presence of 1 mM glutathione and metabolic activation. Rasagiline caused a dose dependent increase in mutant frequency at 50, 75 and 100 ug/ml. Evaluation of colony sizes at the high doses (the only rasagiline doses evaluated) suggested that there was an increase in the proportion of small colonies in the presence of metabolic activation. No particular changes in the proportion of colonies were noted in the absence of metabolic activation. Absolute increases were observed in large and small colony formation, although the absolute increases were larger in small colony formation. These data suggests that rasagiline causes clastogenic changes in treated cell in this assay.

Rasagiline was negative in the in vivo mouse micronucleus assay at doses up to 200 mg/kg (see page 114). This was an appropriate high dose since mortality was observed in mice administered 320 mg/kg in a dose range finding study. Rasagiline was also negative in the unscheduled DNA synthesis assay at 200 mg/kg in rat hepatocytes (see page 117). This assay has not been adequately validated. It should not be discussed in the label.

In summary, rasagiline has been examined in an appropriate battery of genotoxicity studies. Rasagiline increased the incidence of chromosomal aberrations in human peripheral lymphocytes in three separate assays and in the mouse lymphoma assay. It was negative in the Ames assay and in the in vivo mouse micronucleus test.

3.5.4.4 CARCINOGENICITY

Rasagiline has been evaluated for carcinogenic potential in rats and mice. The Executive Carcinogenicity Assessment Committee has evaluated both the protocols for these studies and the results (see appendices).

In the mouse carcinogenicity study, mice were administered 0, 1, 15 or 45 mg/kg for two years (see page 121). The mice tolerated these doses with out notable toxicity. Mortality at the high dose was comparable to control values and body weights were within 10% of control values. A significant positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed in male mice ($p=0.0007$). The increase in combined adenomas/carcinomas was significant in the high dose males ($p=0.0045$). There was also a near significant trend in the incidence of lung carcinomas alone in male mice ($p=0.0065$, FDA significance criteria is $p\leq0.005$ for trend tests) and a near significant increase in the incidence of combined adenomas/carcinomas in mid-dose males ($p=0.04$, FDA significance criteria is $p\leq0.01$ for pair-wise comparisons). Although the increase in mid-dose males was not statistically significant, this reviewer regards this increase as being biologically significant due to the positive response in the high dose. The sponsor suggested that the incidence of lung neoplasms was within historical control

range, but an examination of studies conducted within three years of this study showed that the incidence in the control males was comparable to the control values in the present study. In female mice, a positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed, but the trend was not statistically significant (p=0.0071). An increased incidence of combined lung adenomas/carcinomas was observed in the low and high dose females, but the increase was not statistically significant (p=0.0175 at the high dose). However, the female mice had lower systemic exposure to rasagiline than males (the AUC in high dose females was 5,613 ng-hr/ml compared to 15,673 ng-hr/ml in high dose males) which would lower the probability of detecting tumors in the females. This reviewer feels that the lung neoplasms in females is a biologically significant finding at the mid and high dose due to the positive response in males in the same tissue, the positive genotoxicity studies (see above) and the lower systemic exposure in the study.

In the rat carcinogenicity study, male rats were administered 0, 0, 0.3, 1 or 3 mg/kg for two years; female rats were administered 0, 0, 0.5, 2, 5 or 17 mg/kg for two years (see page 134). The high dose in both sexes exceeded the MTD as indicated by greater than 20% decrements in body weight compared to controls. No significant increase in tumor incidence was observed at the high dose. However, doses which exceed the MTD have lower sensitivity for detecting a tumorigenic response than doses which do not exceed the MTD. In cases in which the high dose exceeds the MTD, the lower dose groups must be fully examined for tumors. In the present study, histopathology was not conducted on the terminally sacrificed rats in the low and mid dose groups. It is FDA policy that if the high dose exceeds the MTD, then histopathology must be conducted on all animals in the lower dose groups. A final conclusion can not be made on the potential carcinogenicity of rasagiline in rats until full histopathology has been conducted on the low and mid dose rats. This reviewer recommends that the sponsor conduct histopathology examinations in the lower dose groups prior to approval of the drug product.

In summary, rasagiline caused a statistically significant increased trend in the incidence of combined lung adenomas/carcinomas in male mice with a significant increase in combined lung adenomas/carcinomas in high dose male mice. A near statistically significant increase in the incidence of combined lung adenomas/carcinomas was observed in female mice. Since a significant increase in the same tumor was observed in male mice and since rasagiline is genotoxic, the increased incidence of lung neoplasms in female mice is considered biologically significant. No significant increase in the incidence of tumors was observed at the high dose in male and female rats. However, the high dose exceeded the maximum tolerated dose and the terminally sacrificed lower dosed rats were not examined histopathologically. A final conclusion on the potential carcinogenicity of rasagiline in rats can not be made until the incidence of tumors in the low and mid dose rats has been evaluated.

3.5.4.5 REPRODUCTIVE TOXICITY

In a male mating and fertility study, rasagiline was administered to rats at 0.5, 2.0 and 5.0 mg/kg/day for 28 days prior to mating (see page 147). The dose was subsequently reduced to 0.3, 1.0 and 3.0 mg/kg due to excessive toxicity (decreased body weight). No adverse effects on fertility were observed. In addition, No effects were

observed on sperm parameters. It was concluded that rasagiline had no effect on parameters affecting male reproductive capacity.

In a combined mating/fertility and embryofetal development study in females, rasagiline was administered at 0.3, 1 or 3 mg/kg for 14 days prior to mating through gestation day 17 (see page 150). This is an appropriate method for combining these studies. The 3 mg/kg dose caused decreased body weight in the rats during the premating period. No effects on body weight gain were noted during the gestation period. Rasagiline did not affect any reproductive parameters (female fertility, fetal development, fetal malformations) in this study. Toxicokinetic evaluations were performed prior to mating (after 14 days of dosing) and on gestation day 17. The AUC(0-8) and Cmax values were increased in pregnant rats by 2-4-fold compared to non-pregnant rats.

Rasagiline was examined for effects on embryo-fetal development in rabbits (see page 156). Rabbits were administered 0, 1, 7 or 45 mg/kg from gestation day 6 through 20. The does administered 45 mg/kg lost about 150 grams body weight during treatment compared to a gains of 150-200 grams in the other groups. Decreased fetal weight and increased embryo-fetal mortality was observed at 45 mg/kg. No adverse effects were observed at 7 mg/kg. This reviewer is concerned about the wide gap between the high dose and the mid-dose. In a preliminary dose range finding study (study — Project 659823, not reviewed in this report), rabbits tolerated a 15 mg/kg dose with no adverse effects while 45 mg/kg caused mortality in 1/5 treated does. The sponsor did not justify the doses used in this study. This reviewer is concerned about the adequacy of the doses used in this study. The high dose in an embryofetal development study should induce mild maternal toxicity. A dose which is frankly toxic, as is the 45 mg/kg dose in the present study, would permit an assessment of whether fetus is at greater sensitivity to drug effects than the parent. Likewise, a high dose which is too low would not permit adequate exposure to the fetus to detect potential teratagenic effects. This reviewer recommends that the sponsor repeat the Segment 2 rabbit study using doses between 7 and 45 mg/kg. This could be done as a Phase IV commitment.

In a prenatal/postnatal reproductive toxicity study, female rats were administered 0, 0.1, 0.3 or 1 mg/kg from gestation day 6 through post partum day 21 (see page 188). The 1 mg/kg dose induced mild maternal toxicity as indicated by a 10% decrease in body weight compared to controls. Increased pup mortality was also observed at 1 mg/kg between post partum days 0 and 4 (viability index) was well as between post partum days 5 and 22 (weaning index). No significant alterations in physical or behavioral development were observed. Fertility in F1 rats was unaffected. The NOEL in this study was 0.3 mg/kg while the LOEL was 1 mg/kg.

In summary, rasagiline has been evaluated in the full reproductive toxicity battery. Rasagiline did not affect fertility parameters in male and female rats at doses up to 3 mg/kg. No adverse effects on embryo-fetal development were observed at 3 mg/kg in rats, a dose which induced mild maternal toxicity. In the rabbit embryo-fetal development study, fetotoxicity (as indicated by decreased fetal weight and increased embryo-fetal deaths) were observed at the frankly maternally toxic dose of 45 mg/kg. No maternal or embryo-fetal effects were observed at 7 mg/kg. It is recommended that this study be repeated as a Phase IV commitment. In the test of post-partum development, 1 mg/kg caused mild maternal and offspring toxicity. No effects were observed on pup physical or behavioral development. In addition, pup fertility was unaffected. Studies on

the potential interaction between rasagiline and sinemet are discussed elsewhere (see page 213).

3.5.4 Rasagiline Interactions with L-DOPA/Carbidopa

A particular concern with drugs for Parkinson's disease is the potential for interactions with Sinemet (L-DOPA/carbidopa). L-DOPA is a dopamine precursor which is used for the symptomatic treatment of advanced Parkinson's disease while carbidopa increases the bioavailability of L-DOPA by inhibiting its metabolism. Virtually all patients whose Parkinson's disease progresses to an advanced state will take Sinemet. It is therefore important that the potential interaction between rasagiline and Sinemet be examined. The sponsor has conducted a series of studies to examine the potential interactions between Sinemet and Rasagiline.

The effects of rasagiline on the pharmacokinetics of leveodopa/carbidopa has been examined in rats (see page 52). Rats were administered 40/10 mg/kg levodopa/carbidopa with or without 1 mg/kg rasagiline po. The pharmacokinetics of levodopa were determined on days 1 and 7. There did not appear to be any significant pharmacokinetic interactions. Likewise, combination toxicology studies (see below) did not suggest that there is a significant effect on levodopa plasma levels.

In a dose range finding study, rats were administered 0, 0.3, 1.0 or 3.0 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) for four weeks (see page 61). Additional groups were treated with vehicle, 3 mg/kg rasagline alone or sinemet alone. Rats did not tolerate the combination of 3 mg/kg rasagiline with sinemet, so the high rasagiline dose was lowered on Day 12 to 2 mg/kg rasagiline in both the combination group and the rasagiline alone group. Despite this, 6/10 male rats and 2/10 female rats were killed in extremis or died between study days 24 and 32. One male rat administered 1 mg/kg rasagiline with sinemet was killed in extremis on day 27. Rats exhibited signs of illness including ataxia, thinness, prostrate posture and hypoactivity. Significantly decreased body weight was observed in males administered 3/2 mg/kg rasagiline with sinemet. An increase in AST values (about 5X control values) and ALT values (about 2X control values) were observed in female rats treated with 3/2 mg/kg rasagiline with sinemet, but changes in male rats were less than 1.5X control values. There were no significant histopathological changes observed in the liver of these rats. Relative spleen and thymus weights were reduced in rats treated with the combination of 3/2 mg/kg rasagiline with sinemet, but no histological changes were noted. No significant changes were noted in hematology or urinalysis examinations. Rasagiline and sinemet alone had no significant adverse effects alone.

In a 13 week study, rats were administered 0, 0.1, 0.25, 0.5 or 1 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) (see page 69). Additional groups were treated with vehicle, 1 mg/kg rasagline alone or sinemet alone. Increased mortality was observed in 1 mg/kg combination group (5/10 males and 1/10 females compared to no mortality in control groups). Body weights were decreased in rats receiving 0.5 or 1 mg/kg rasagiline in combination with levodopa. No significant effects were observed on gross pathology or histopathology. Rasagiline had no significant effect on levodopa levels, but levodopa decreased rasagiline the Cmax (by about 60% in both sexes) and AUC (by 32% and 25% in males and females, respectively). It is concluded that the combination of rasagiline and sinemet induced toxicity which was not observed in rats dosed with either drug alone. Adverse effects were observed at 1 mg/kg

rasagiline in combination with sinemet whereas rats tolerated rasagiline doses as high as 5.1 mg/kg for 26 weeks.

In a 13 week study, dogs were administered 0, 0.3, 1 or 2 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) (see page 87). Additional groups were treated with vehicle, 2 mg/kg rasagline alone or sinemet alone. The combination of 2 mg/kg rasagiline with sinemet caused circling behavior in dogs (4/12 dogs), which may be a sign of stereotypic behavior. In addition, one dog in this group was humanely sacrificed during week 12 of the study. One out of eight dogs in the combination of 1 mg/kg rasagiline with sinemet had circling behavior. Emesis was reported in all dogs receiving levodopa/carbidopa. Decreased body weight gain was observed in dogs treated with sinemet, which was probably related to levodopa-induced emesis. No effects on hematology, clinical chemistry, gross pathology or histopathology were observed. No significant interactions were observed on the toxicokinetics of sinemet and rasagiline. It is concluded that the combination of rasagiline and sinemet induced toxicity which was not observed in dogs dosed with either drug alone. Adverse effects were observed at 2 mg/kg rasagiline in combination with sinemet whereas dogs tolerated rasagiline doses as high as 21 mg/kg for 52 weeks.

The genotoxicity of the combination of rasagiline with sinemet was examined in an in vivo mouse micronucleus assay. Mice were administered 25, 50 or 100 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) (see page 119). No increase in the incidence of micronuclei was observed in the bone marrow of mice sacrificed 24 or 48 hours after treatment.

In an embryo-fetal development study, rats were administered 0, 0.1, 0.3 or 1 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) (see page 164). Additional rats received 1 mg/kg rasagiline or sinemet alone. The combination of 1 mg/kg rasagiline with sinemet induce slight maternal toxicity as indicated by decreased body weight gain. The combination of rasagiline and sinemet did not affect embryo-fetal development.

In an embryo-fetal development study, rabbits were administered 0, 0.1, 0.6, 1.2 or 3 mg/kg rasagiline with 100 mg/kg sinemet (80 mg/kg L-DOPA/20 mg/kg carbidopa) (see page 176). Additional rabbits received 3 mg/kg rasagiline or sinemt alone. Rabbits did not tolerate the combination of 3 mg/kg rasagiline with sinemet; 13/22 rabbits died or were sacrificed moribund. Decreased body weight was observed in rabbits treated with the combination of sinemet with 0.1, 0.6 or 1.2 mg/kg rasagiline. Increased total postimplantation loss was observed in rabbits treated with the combination of sinemet with 0.6 or 1.2 mg/kg rasagiline. The combination of rasagiline and sinemet did not affect embryo-fetal abnormalities.

It is concluded that the combination of rasagiline and sinemet results in increased toxicity in rats, dogs and rabbits. The effects do not appear to be due to increased levels of either rasagiline or levodopa themselves. It is probable that the effects are due to increased dopamine levels resulting from increased availability of the dopamine precursor levodopa combined with decreased dopamine catabolism from inhibition of MAO. No additional target organs were identified in these studies.

5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

3.5.5 Recommendations

The sponsor has submitted studies that address most of the preclinical needs for drug approval. There are two deficiencies in the data that the sponsor needs to address prior to approval.

1. The sponsor has not adequately evaluated the carcinogenic potential of rasagiline in rats. The sponsor has submitted a two year carcinogenicity study in rats. The high dose in this study exceeded the maximum tolerated dose and did not show carcinogenic potential. The low and middle doses were not evaluated histopathologically. The sponsor needs to conduct and submit histopathological analysis on the low and mid-dose groups in this study to make this a valid study.
2. The sponsor has not characterized the circulating metabolites of rasagiline in the test species. The sponsor needs to provide estimates of circulating metabolites in mice, dogs and rats.

An additional concern identified in this review is that the sponsor has not adequately examined the potential toxicity in the embryo-fetal development study in rabbits. It is recommended that the sponsor repeat the study as a Phase IV commitment using doses between 7 and 45 mg/kg/day.

Based on these considerations, this reviewer considers this application to be **Approvable.**

3.6 APPENDIX/ATTACHMENTS

3.6.1 Executive Carcinogenicity Assessment Committee Meeting Minutes-Mouse Protocol

Executive CAC
Feb. 10, 1998

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Ken Hastings, Ph.D., HFD-880, Alternate Member
Thomas Steele, Ph.D., HFD-120, Presenting Reviewer
Glenna Fitzgerald, Ph.D., HFD-120, Division Team Leader

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

IND #45958
Rasagiline
Teva Pharmaceuticals

Background

Dose Selection for Mouse Study

The sponsor is requesting CAC comment on dosage selection for a mouse carcinogenicity study. Proposed doses are 1, 15 and 45 mg/kg/day of rasagiline (calculated as base).

The sponsor's high dose selection was based on a combination of toxicological, pharmacokinetic and pharmacodynamic considerations. Toxicity findings in a 13-week gavage study of up to 100 mg/kg/day rasagiline included suppression of body weight gain (not dose-related), and thymic necrosis at 100 mg/kg, most notable in females. The pharmacokinetic changes observed were possible saturation of metabolism and/or elimination at ≥ 45 mg/kg/day. The pharmacodynamic endpoint was a loss of rasagiline's selectivity for MAO-B vs. MAO-A at ≥ 20 mg/kg; the sponsor suggests that this will lead to "imbalances of many hormonal and neuronal systems and alteration of the mouse physiology."

Because there was not a clear dose-relationship for suppression of body weight gain, the reviewer did not consider the body weight gain data useful for dosage selection. The committee concluded that the general trend for weight gain suppression suggested that the 60 and 100 mg/kg doses in the 13-week study may exceed the MTD. The findings of thymic necrosis supported the use of the toxicity endpoint. Thus, the committee concurred with the sponsor's selection of 45 mg/kg as the high dose.

The committee did not agree with the sponsor's pharmacokinetic or pharmacodynamic arguments. Metabolism did not appear to be saturated as the amount of metabolite increased proportionally to dose between 45 and 60 mg/kg. Moreover, saturation of systemic absorption as measured by saturation of exposure, not saturation of metabolism is the ICH accepted high dose selection endpoint. The loss of selectivity for MAO-B vs. MAO-A is not expected to result in a condition that would severely impair mouse physiology as stipulated in the ICH guidance (e.g. blood loss, hypotension).

The committee felt that the low dose should provide an exposure a few fold of human and based on analysis of the available data and the currently recommended human dose, a LD from 1 mg/kg could achieve this. This is based on assumptions of a linear extrapolation of exposure form the range of doses tested and minimal increases in the clinical dose from that currently estimated by the sponsor. There was also discussion regarding the large spread between the mid and low dose (15-fold), and the potential complications for evaluation of human risk which could result in if tumors were observed at the mid dose but not the low dose. There was thus, discussion regarding recommending some increase in the low dose to address both potential concerns.

Executive CAC Recommendations and Conclusions:

1) The committee concurs with the sponsor's proposed high dose selection of 45 mg/kg/day based on MTD (body weight gain selection, thymic necrosis), and the proposed MD of 15 mg/kg.
2) Based on currently available information, the committee felt that the proposed LD of 1 mg/kg was adequate. The sponsor, however, may want to reevaluate the LD selection based on the above discussed considerations and the likelihood of increases in the therapeutic dose.

3.6.2 Executive Carcinogenicity Assessment Committee Meeting Minutes-Rat Protocol

Executive CAC
May 27, 1997

Committee: Robert Osterberg, Ph.D., HFD-520, Acting Chair
Albert DeFelice, PhD, HFD-110, Alternate Member
James Farrelly, Ph.D., HFD-530, Alternate Member
Ronald Steigerwalt, PhD, HFD-510, Alternate Member
Barry Rosloff, PhD, HFD-120, Acting Division Team Leader
Lillian Patrician, MS, MBA, HFD-024, Project Manager
Thomas Steele, PhD, HFD-120, Presenting Reviewer

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

IND 45,958 (Steele/Rosloff; HFD-120)
Rasagiline mesylate - proposed protocol for rat CA study
TEVA Pharmaceuticals

The current proposal is a revision of a protocol that was reviewed by the Exec CAC on November 7, 1995. The original protocol called for doses of 0.3, 1, and 3 mg/kg, by gavage, in both sexes. The committee concurred with proposed doses for male rats based on decreased weight gain in earlier studies. Females were less susceptible to this effect and would likely tolerate higher doses. Thus, the committee did not concur with the proposed doses for female rats, nor could they recommend alternative doses due to a lack of sufficient data in the dose range-finding study.

The sponsor responded with proposals of 0.5, 2, and 5 mg/kg for males, and 0.5, 2, 5, and 10 mg/kg for females. The sponsor used "pharmacokinetic considerations" as a basis for their proposal. The reviewer indicated that the drug is clastogenic; therefore, pharmacokinetic methods are not appropriate for dosage selection. However, the high dose of 17 mg/kg caused a 10% reduction in female rat body weights in the 6-month study. The reviewer recommended that the high dose selection for females should be based on this finding. The reviewer recommended that the originally proposed male rat doses, which had already received concurrence from the committee, should be used since doses of 2 and 5 mg/kg may reduce body weights by greater than 10%.

Executive CAC recommended 0.3, 1, and 3 mg/kg for male rat dosing. Female rats should be dosed at 0.5, 2, 5, and 17 mg/kg.

The committee was also asked to comment on the sponsor's proposal to use group housing in the rat carcinogenicity study since the 6-month study was conducted under group housing conditions. The committee recommended that carcinogenicity studies should be conducted using individual housing conditions.

Robert Osterberg, Ph.D.
Acting Chair, CAC

cc: /Div File (IND 45,958), HFD-120
/OFitzgerald, HFD-120
/Tsteele, HFD-120
/LPatrician, HFD-024

3.6.3 Executive Carcinogenicity Assessment Committee Meeting Minutes-Final Mouse and Rat Studies

Executive CAC
June 8, 2004

Committee: Abby Jacobs, Ph.D., HFD-540, Acting Chair
Joseph Contrera, Ph.D., HFD-900, Alternate Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Lois Freed, Ph.D., HFD-120, Team Leader
Paul Roney, Ph.D., HFD-120, Presenting Reviewer

Author of Minutes: Paul Roney, Ph.D.

NDA 21-641
Drug Name: Rasagiline (Agilect)
Sponsor: Teva Pharmaceuticals

Mouse Carcinogenicity Study
CD-1 mice were administered rasagiline orally (by gavage) at doses of 0, 1, 15 or 45 mg/kg for two years. The mice tolerated these doses without notable toxicity. Mortality at the high dose was comparable to control values and final mean body weights were within 10% of control values. A significant positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed in male mice ($p=0.0007$). The increase in combined adenomas/carcinomas was significant in the high dose males ($p=0.0045$). There was also a near significant trend in the incidence of lung carcinomas alone in male mice ($p=0.0065$, FDA significance criteria is $p\leq0.005$ for trend tests) and a near significant increase in the incidence of combined adenomas/carcinomas in mid-dose males ($p=0.04$, FDA significance criteria is $p\leq0.01$ for pair-wise comparisons). The sponsor suggested that the incidence of lung neoplasms was within historical control range, but an examination of studies conducted within three years of this study showed that the incidence in control males was comparable to the control values in the present study. This would suggest that the increase in lung neoplasms observed in this study is above the historical control range as well. In female mice, a positive trend in the incidence of lung neoplasms (adenomas/carcinomas combined) was observed. The trend was not statistically significant ($p=0.0071$); however, female mice had lower systemic exposure to rasagiline than males (the AUC in high dose females was 5,613 ng-hr/ml compared to 15,673 ng-hr/ml in high dose males) which would lower the probability of detecting tumors in females. It did not appear that an MTD was achieved in females.

Rat Carcinogenicity Study
Rasagiline was administered orally (by gavage) at doses of 0, 0, 0.3, 1 or 3 mg/kg in male Sprague-Dawley rats and at doses of 0, 0, 0.5, 2, 5 or 17 mg/kg in female Sprague-Dawley rats for two years. The high dose in both sexes exceeded the MTD as indicated by greater than 20% decrements in mean body weight compared to controls. No significant increase in tumor incidence was observed at the high dose. Histopathology was not conducted on a full battery of tissues in terminally sacrificed rats in the low and mid dose groups.

Executive CAC Recommendations and Conclusions:

Mouse carcinogenicity study: the Committee agreed that the mouse study was adequate, and concluded that the mouse study was positive for tumors in males (increased incidence of combined lung adenoma/carcinoma). There was an increase in the incidence of lung adenoma/carcinoma in females. Although the increase was not statistically significant, the Committee concluded that the finding in females should not be dismissed considering the increase in the same tumor types in male mice.

Rat carcinogenicity study: the Committee agreed that the rat study was adequate. However, the Committee could not reach a final conclusion regarding the rat study, because the high dose was associated with an excessive effect on body weight (i.e., >10% decrease in mean body weight compared to controls) in both males and females and complete histopathology was not done on the low and mid-dose groups. The Committee recommended that the sponsor conduct histopathology on the low and mid-dose groups and submit the results for evaluation.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

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/Division File, HFD 120
/LFreed, HFD-120
/PRoney, HFD-120
/TWheelous, HFD-120
/ASeifried, HFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Roney
6/29/04 09:04:39 AM
PHARMACOLOGIST

Lois Freed
7/1/04 12:19:41 PM
PHARMACOLOGIST
Please see supervisory memo.