

**In the above table, hallucinations was the only adverse event to show a potential effect for gender, with the relative risk elevated for female subjects treated with rasagiline and reduced for male rasagiline-treated subjects (compared to female and male placebo subjects, respectively). For the three placebo-controlled trials, gender-stratified occurrence of hallucinations is summarized below:

FDA Table 51: Number and Percent of Subjects Experiencing Hallucinations by Sex in TEMPO, LARGO and PRESTO

Hallucinations By Study	Rasagiline 1 mg				Placebo				Relative Risk*	
	Female		Male		Female		Male		Female	Male
	N	%	N	%	N	%	N	%		
PRESTO	5/50	10	1/99	1.0	1/55	1.8	4/104	3.8	5.6	0.3
LARGO	1/77	1.3	4/154	2.6	0/97	NA	3/132	2.3	NA	1.1
TEMPO	0/44	NA	1/90	1.1	1/58	1.7	1/74	1.4	NA	0.8

Although a potential effect of gender on the occurrence of hallucinations was suggested by the pooled data from Cohort 2, analysis of the individual studies shows that the signal comes only from the North American adjunctive trial. The signal for an excess of hallucination in women compared to men is not supported by the data from the monotherapy trial.

4.7.2 Age

Cohort 1 (Placebo-controlled rasagiline monotherapy): The sponsor noted an increased incidence of AEs in geriatric subjects (age 65 or over) on rasagiline (1 mg) compared to placebo for accidental injury, angina pectoris, increased cough and rash (ISS 6.4.1.1).

FDA Table 52: Number and Percent of AEs in Geriatric and Non-Geriatric Patients in Cohort 1 (Adapted from Sponsor Post-Text Table 77)

Adverse Event	Rasagiline 1 mg (N=149)				Placebo (N=151)				Relative Risk*	
	Age < 65 (N=85)		Age > 65 (N=64)		Age < 65 (N=86)		Age > 65 (N=65)		Age < 65	Age > 65
	N	%	N	%	N	%	N	%		
Accidental Injury	5	5.9	7	10.9	8	9.3	7	10.8	0.63	1.0
Angina Pectoris	0	NA	2	3.1	0	NA	0	NA	NA	NA
Increased Cough	2	2.4	5	7.8	5	5.8	3	4.6	0.4	1.7
Rash	1	1.2	2	3.1	3	3.5	2	3.1	0.3	1.0

*Relative Risk was calculated as the risk (percent) of the specific AE for each age category in the rasagiline group divided by the percent for the same age category in the placebo group.

In the above table, increased cough was the only adverse event to show a potential effect for age, with the relative risk reduced for subjects treated under 65 treated with rasagiline and elevated for rasagiline-treated subjects over age 65. However, based on a small

number of cases, when the age-stratified risk of increased cough in the three placebo-controlled trials (TEMPO, PRESTO and LARGO) was examined, this trend was not replicated.

Cohort 2 (Placebo-controlled rasagiline as levodopa adjunct): The sponsor stated that when analyzed for differences in AE incidence related to age, and not similar in placebo, rasagiline-treated participants under age 65 had more accidental injury, hypotension, vomiting, paresthesia, rash and skin disorder (ISS 6.4.1.2). They note that geriatric subjects receiving rasagiline had an increased postural hypotension, hallucinations, and sleep disorder (See table below).

FDA Table 53: Incidence of AEs by Body System and COSTART Terms in Geriatric and Non-Geriatric Patients in Cohort 2 (Adapted from Sponsor Post-Text Table 79)

Adverse Event	Rasagiline 1 mg (N=149)				Placebo (N=151)				Relative Risk*	
	Age < 65		Age > 65		Age < 65		Age > 65		Age < 65	Age > 65
	N	%	N	%	N	%	N	%		
Accidental Injury	23	11.3	8	4.5	7	3.8	13	6.4	3.0	0.7
Hypotension	7	3.4	1	0.6	3	1.6	4	2.0	2.1	0.3
Postural Hypotension	7	3.4	11	6.2	2	1.1	3	1.5	3.1	4.1
Sleep Disorders	5	2.5	11	6.2	2	1.1	6	3.0	2.3	2.1
Hallucinations	2	1.0	9	5.1	2	1.1	6	3.0	0.9	1.7
Vomiting	10	4.9	3	1.7	1	0.5	3	1.5	9.8	1.1
Paresthesia	6	3.0	1	0.6	3	1.6	3	1.5	1.9	0.4
Rash	8	3.9	2	1.1	3	1.6	3	1.5	2.4	0.7
Skin disorder	5	2.5	0	NA	3	1.6	3	1.5	1.6	NA
Constipation ⁸⁹	5	2.5	11	6.2	2	1.1	6	3.0	2.3	2.1

*Relative Risk was calculated as the risk (percent) of the specific AE for each age category in the rasagiline group divided by the percent for the same age category in the placebo group.

In the above table, accidental injury, hypotension, paresthesia and rash were the adverse events to show a potential effect for age, with the relative risk elevated for rasagiline-treated subjects under age 65, and reduced for rasagiline-treated subjects over age 65. However, based on a small number of cases, when the age-stratified risk for these adverse events was examined in the three placebo-controlled trials (TEMPO, PRESTO and LARGO), this trend was not replicated. Subjects under age 65 also seemed to be more likely to report vomiting than older subjects.

⁸⁹ I also included constipation, which was listed in Post-Text Table 79 but not mentioned in the sponsor's written summary of the table.

4.8 Drug-Drug Interaction

In section 6.10 of the ISS, Teva presents data on AEs in Cohort 2 (LARGO and PRESTO) stratified by use of the following concomitant medications: dopamine agonists, entacapone, amantadine, antidepressants and an anxiolytic/sedative/hypnotic or neuroleptic agent.⁹⁰ The sponsor stated that the drugs selected for additional analyses were those prescribed frequently or of interest due to their expected pharmacological effects (ISS 6.10). Sponsor tables displaying differences in AEs (in descending order) with and without these concomitant medications are provided in Attachments 9.16, 9.17, 9.18, 9.19 and 9.20 of this review.

4.8.1 Concomitant Dopamine Agonists

Teva reports that addition of dopamine agonists yielded a small increase in dopaminergic adverse events for subjects receiving rasagiline 1 mg, in comparison with placebo (Attachments 9.16 of this review). The sponsor suggests this would be expected by the intrinsic dopaminergic properties of rasagiline (ISS 6.10.1). The sponsor states that rash, skin disorders and extrapyramidal syndrome were reported in the rasagiline treatment group only in participants receiving dopamine agonists. In addition, hallucinations and peripheral edema were seen primarily with combined treatment (ISS 6.10.1).

Reviewer comment: *In Attachments 9.16 of this review, the relative risk of hallucinations in subjects treated with a concomitant dopamine agonist was 3.3 (4% in rasagiline subjects with dopamine agonist/1.2% in placebo subjects with dopamine agonists), compared to a relative risk of 0.24 (0.8%/3.4%) in subjects not receiving concomitant dopamine agonists.*

4.8.2 Concomitant Entacapone

The sponsor states that for rasagiline-treated subjects more reports of dyskinesia, dizziness, weight loss, and anorexia were seen in the presence of entacapone (ISS 6.10.2) (Attachments 9.17). For placebo subjects, reports for dyskinesia were also higher with concomitant entacapone (14.8% with entacapone compared to 7.1% without), but fewer of the other dopaminergic AEs were reported in placebo subjects using entacapone.

4.8.3 Concomitant Amantadine

Teva reports that dyskinesia, extrapyramidal syndrome, dry mouth, vomiting and dizziness were reported more frequently in rasagiline subjects who received amantadine, compared to rasagiline subjects not exposed to amantadine. In addition, the percentage of subjects reporting these AEs was higher in rasagiline subjects receiving amantadine than in placebo subjects receiving amantadine (ISS 6.10.3) (Attachments 9.18).

⁹⁰ The sponsor stated that as too few patients (about 5% in each treatment group) received sympathomimetic agents (which were not allowed in both studies), a table was not provided for this drug group.

4.8.4 Concomitant Antidepressants

Due to previous reports of severe AEs associated with the combination of other MAO inhibitors and antidepressants, use of antidepressants in the rasagiline development program was restricted to selected low-dose SSRIs in the PRESTO study. The sponsor states that accidental injury, depression, anorexia, back pain and dry mouth were the AEs with the largest increase in occurrence for subjects treated with SSRIs and rasagiline, compared to participants not treated with SSRIs (Attachments 9.19). However, Teva states that while relatively few subjects (N=23) were treated with rasagiline and SSRIs, no symptoms of serotonin syndrome were reported with their concomitant use.

Reviewer comment: *In the proposed labeling, the sponsor makes the following statement regarding the use of SSRIs with rasagiline:*



This reviewer suggests that the statement be modified in the following ways. First, as noted above, the development program protocols significantly limited the concomitant administration of antidepressants with rasagiline. Although the statement includes descriptions of dose ranges, the use of these dose restrictions should be more clearly stated. Secondly, the phrase ————— should be replaced by the specific number of subjects exposed to rasagiline and the antidepressant.

4.8.5 Concomitant CYP 1A2 Inhibitors or Substrates

As CYP 1A2 is the enzyme primarily responsible for rasagiline metabolism, Teva investigated the co-administration of medications affecting the same enzyme. The sponsor states that when ciprofloxacin 500 mg,⁹¹ a CYP 1A2 inhibitor, was administered twice daily to healthy volunteers receiving rasagiline 2 mg/day there was no indication of an increase in the frequency or severity of adverse events (ISS 12.3.1). The sponsor recommends, however, that as a general precaution “care must be taken when rasagiline is co-administered with compounds that inhibit CYP 1A2.” (ISS 12.3.1)

Teva stated that co-administration of theophylline, a CYP 1A2 substrate, likewise gave no indication of an increase in the frequency or severity of adverse events (ISS 12.3.2) As the sponsor observed no pharmacokinetic interaction between theophylline and rasagiline, no dose adjustment was advised (ISS 12.3.2).

4.9 Overdose

⁹¹ While the exact degree to which this dose of ciprofloxacin would inhibit CYP 1A2 was not specified in the ISS summary, this dosage would be an acceptable choice for a co-administration study as it is a commonly used dosage in clinical practice.

In the proposed labeling and the ISS, Teva states that no cases of rasagiline overdose in humans were reported during the development program.⁹² As rasagiline has not yet been marketed anywhere in the world, there are no post-marketing reports of overdose.

Although not technically an overdose, Teva did study rasagiline in a single-dose study in healthy volunteers receiving up to 20 mg/day, as well as in a ten-day study of healthy volunteers receiving 10 mg/day (ten times the intended dose). (See clinical pharmacology section 4.5.1 of this review for the details of these exposures.)

The sponsor notes that although rasagiline overdose has not been observed, experience with other selective MAO inhibitors in overdose suggests that significant non-selective inhibition of both MAO-A and MAO-B may occur. Teva's proposed labeling recommends monitoring and supportive treatment (ISS 12.6).

4.10 Withdrawal

The sponsor reports that clinical trials have not revealed evidence for potential abuse, tolerance or physical dependence; however, the trial designs did not specifically include post-discontinuation follow-up procedures to ascertain withdrawal symptoms (ISS12.7). Teva states that studies conducted in rodents likewise did not demonstrate potential for abuse or dependence. The sponsor notes that systematic studies in humans designed to evaluate abuse potential have not been performed, and studies specifically addressing withdrawal were not submitted (ISS 12.7). A search for the AE keyword "withdrawal" in the Cohort 9 (all subjects treated with rasagiline) dataset did not identify any AEs associated with rasagiline withdrawal.

Reviewer comment: The study reports for the three placebo-controlled trials (TEMPO, LARGO and PRESTO) did not describe any method for detecting potential withdrawal symptoms in a prospective fashion.

4.11 Drug Disease Interaction

With the exception of renal and hepatic impairment,⁹³ Teva did not present data on drug-disease interactions within the rasagiline development program.

5.0 Special Safety Issue: Melanoma

5.1 Materials Reviewed

This review is based upon information contained within the following documents:

Sponsor Submissions:

⁹² No cases of overdose occurring subsequent to the ISS data collection date were given in the 120 Day Safety Update.

⁹³ Presented in Section 2.3 of this review.

- NDA 21-641 (Rasagiline), Submitted September 2003
- Assessment of Melanoma in the Rasagiline Clinical Program and in the General PD Population, submitted as ISS Appendix 18.3 within the Rasagiline NDA. Prepared by Dr. Noa Leibovitch.
- Cancer incidence among patients with Parkinson's disease: a nationwide cohort study in Denmark. Internal submitted as ISS Appendix 18.3, Attachment 3, within the rasagiline NDA. Prepared by _____
- Malignant melanoma: evaluation of association of Parkinson's disease in patients with history of melanoma, submitted as ISS Appendix 18.3, Attachment 4, within the rasagiline NDA. Prepared by Dr. Darrell Rigel.
- Malignant Melanoma: Evaluation of mix of in situ versus invasive lesions with pathology laboratory confirmation, submitted as ISS Appendix 18.3, Attachment 5, within the rasagiline NDA. Prepared by Dr. Darrell Rigel.
- Malignant Melanoma in the Rasagiline Development Program, submitted by Teva, June 28, 2001.
- Melanoma and Rasagiline Therapy, Review of 5 Cases and Analysis of a Possible Relationship, submitted by Teva June 2, 2001, prepared by Dr. Darrell Rigel.

Prior FDA Reviews:

- Review and Evaluation of Clinical Data: Information on Five Melanoma Cases, dated 4/18/2001. Prepared by Dr. Kevin Prohaska, FDA/CDER/DNDP.
- Review and Evaluation of Clinical Data: Information on Five Melanoma Cases, dated 8/15/2001. Prepared by Dr. Kevin Prohaska, FDA/CDER/DNDP.
- Review and Evaluation of Clinical Data for Malignant Melanoma in the Rasagiline Clinical Development Program, dated 9/21/2001. Prepared by Dr. David Gan, FDA/CDER/DNDP.
- Review and Evaluation of Clinical Data for Malignant Melanoma in the Rasagiline Clinical Development Program, dated 10/17/2001. Prepared by Dr. David Gan, FDA/CDER/DNDP.
- OPDRA Postmarketing Safety Review: malignant melanoma in anti-Parkinsonian agents, dated 5/14/2001.

5.2 Introduction

5.2.1 Background Timeline

In November 2000, the sponsor stated that the occurrence of a fourth case of melanoma during the rasagiline clinical development program prompted their active investigation of the issue. On December 8, 2000, Teva issued a "Dear Doctor" letter to all North American investigators participating in rasagiline trials (Appendix 18.3, pg. 9). An IND safety report (Serial Number 133) describing the four cases was also submitted.

By February 2001, Teva asked North American investigators to modify their Informed Consent to include a discussion regarding melanoma, and the Investigator's Brochure was also updated (NDA Appendix 18.3, Pg. 9).

On March 22, 2001, a fifth melanoma case was reported to Teva. On April 6, 2001, a teleconference was held between Teva and the FDA Division of Neuropharmacological Drug Products (DNNDP), during which the sponsor informed the FDA that they were investigating the matter with the assistance of an epidemiological consultant (Dr. — — — — —), and consultants with expertise in melanoma (Dr. Darrell Rigel, and Dr. DuPont Guerry). Reports by the consultants were submitted to the division on June 28, 2001 (NDA Appendix 18.3 pg. 10). The sponsor also submitted a report (serial number 146) to the FDA, dated April 9 2001, outlining the initial five cases.*

In July 2001, a sixth case of melanoma was identified. At the time of their diagnosis, the initial six participants had all been enrolled in the study TEMPO (TVP-1012/232) (a phase III North American monotherapy trial) or its extension (Study 233). In August 2001, during a teleconference held between Teva and the DNNDP, it was agreed that dermatologic examinations (occurring every three months) would be implemented in all ongoing trials in the United States. Teva also agreed to update the FDA periodically on the status of the melanoma monitoring within the trials (NDA Appendix 18.3 pg. 10).

Dermatologic examinations of participants commenced from October to December 2001 and continued periodically through July 2003. The two adjunctive therapy studies were already ongoing when routine skin examinations began, and Teva estimates only about 42% to 44% of participants had their baseline evaluation prior to treatment initiation (NDA Appendix 18.3, pg. 25). No participants from the TEMPO extension (Study 233) were able to be screened before treatment. As of July 14, 2003, 1228 patients had undergone skin examination in all ongoing trials at least once, representing about 83% of patients participating in trials. A total of 3547 examinations were performed, and 416 biopsies taken in 244 patients (NDA Appendix 18.3, pg. 27).

After institution of the dermatologic examinations, an additional 14 cases were diagnosed (Appendix 18.3 pg. 10). The twenty total melanomas were distributed among the three pivotal studies as follows:

- **Nine cases (in eight subjects) in TEMPO** (North American rasagiline monotherapy). One case occurred during the initial placebo-controlled phase, one during the active-controlled phase, and six additional cases in the TEMPO extension (Study TVP-1012/233). All were in rasagiline-treated participants.
- **Eight cases in PRESTO** (North American levodopa (LD) adjunct). Four cases occurred in the placebo-controlled initial phase of PRESTO (TVP-1012/133), one prior to treatment and three in rasagiline-treated subjects. Four cases were found in the PRESTO extension trial (TVP-1012/135), all in subjects receiving rasagiline.
- **Three cases in LARGO** (Europe/Argentina/Israel LD adjunct). Two of the cases were identified prior to treatment initiation, and the third was in a placebo-treated participant.

* Review and Evaluation of Clinical Data: Information on Five Melanoma Cases, dated 4/18/2001.
Prepared by Dr. Kevin Prohaska, FDA/CDER/DNNDP

5.2.2 Prior FDA Review

5.2.2.1 FDA review of June 2001 sponsor submission: Malignant Melanoma in the Rasagiline Development Program

Dr. David Gan (FDA, Division of Neuropharmacological Drug Products) reviewed the sponsor's analysis of the five initial cases presented in the Teva report titled, "Malignant Melanoma in the Rasagiline Development Program," dated June 28, 2001. In this document the sponsor compared the rate of melanoma in the rasagiline development program to the expected rate of melanoma in the general population (through use of the SEER database, described in Section 3.3.1.1 of this review.)

In addition, comparison was made to a population of PD patients participating in clinical trials, as drawn from the Parkinson's Study Group (PSG), a non-profit group of physicians and other health care providers from medical centers in the United States and Canada (<http://www.parkinson-study-group.org>).

Teva derived the overall patient years of exposure to rasagiline by summing each individual patient's duration of exposure (for white participants only), stratifying person-years (PYs) by age and sex.

5.2.2.1.1 Observed to Expected Comparison with SEER data

To calculate the expected number of cases, the sponsor applied age-specific invasive melanoma incidence rates from SEER to the rasagiline development program population (869 person-years of rasagiline exposure). This yielded an expected case number of 0.392. The sponsor also corrected the possible underreporting to SEER by 125%, 150%, 200% and 300% in their calculations. Ninety five percent Exact Poisson Confidence intervals for observed/expected ratio were calculated (Dr. Gan's FDA review, 9/21/2001).

The reference risk for *invasive* melanoma by age and gender was calculated from the SEER data. The following table contains the sponsor's analysis of the two cases of invasive melanoma observed up to that point (at the time of the June 2001 melanoma report) compared to the expected number of cases as calculated in SEER.

FDA Table 54: Melanoma observed to expected ratio within the rasagiline development program for cases at time of June 2001 melanoma report

Observed/Expected Analysis using SEER Rates			
2 Invasive Cases Observed (Melanoma Report – June 2001)			
Expected Number	Obs/Exp Ratio	P Value	95% CI
0.392	5.1	0.06	0.62,18.43
0.490	4.1	0.09	0.49,14.74

(1.25 x SEER)			
0.588 (1.5 x SEER)	3.4	0.12	0.41,12.29
0.784 (2 x SEER)	2.6	0.19	0.31,9.22
1.176 (3 x SEER)	1.7	0.33	0.21,6.14

5.2.2.1.2 Observed to Expected Comparison with PSG data

The PSG database was searched for studies which met the following criteria:

1. Had six months or more of exposure with at least 100 patients enrolled;
2. Used AE surveillance that should have captured cases of melanoma;
3. Stored data in a searchable electronic format;
4. Used randomization for drug assignment, and
5. Were initiated after 1990

Three studies fulfilled these criteria: the ROADS, CALM-PD, and ELLDOPA. In the ROADS study, patients with early PD were randomized to lazabemide or placebo, and followed for up to one year. In the CALM-PD study, patients with early PD were randomized to pramipexole or levodopa and followed for up to four years. In the ELLDOPA study, patients were randomized to levodopa or placebo and followed for up to 0.8 years. Among the three studies there were 1296 patient-years (PYs) of exposure. It is unclear if the total PYs included the placebo group. No age distribution was reported.

Three cases of melanoma were found in the 1296 PYs from the three PSG studies, compared to the five cases (two invasive and three in situ) in 869 PYs of rasagiline exposure. Dr. Gan calculated an incidence density ratio (IDR) using the incidence density in the rasagiline study group as a numerator and the incidence density in the reference group as a denominator.⁹⁴

Overall, the melanoma incidence density (rate) for the five rasagiline cases known at that time was 5.8 per 1000 PYs, compared to 2.3 per 1000 PYs in the PSG. The IDR for was 2.5 (90% CI:0.75, 8.3, 95% CI:0.60, 10.48).

5.2.2.1.3 Discussion and Conclusions of prior FDA analysis

Dr. Rigel, a consultant for the sponsor, noted that in all five melanoma cases the participant had a history of melanoma risk factors, and that for two of the participants the melanoma was likely a preexisting condition. At the time of the June 2001 report, the sponsor concluded that due to surveillance bias and confounding by melanoma risk

⁹⁴ The sponsor's analysis excluded one of the five cases of melanoma, stating that as only 2.5 months had elapsed between initiation of rasagiline treatment and diagnosis of advanced melanoma, the case must have pre-dated rasagiline treatment. The FDA reviewer included this case in his analysis.

factors (especially increasing age), the number of cases of melanoma in the rasagiline development program did not represent a signal of concern.

Dr. Gan's comments on the sponsor's assessment included that the exact mechanism of melanoma development has not been fully elucidated, nor has the interplay of various risk factors. He further notes that determining causality on an individual case basis, as attempted by the sponsor's consultant, is a difficult task.

Discussion within DNDP lead to the recognition that further analysis would be aided by a better estimation of melanoma background rates within the population of PD trial participants. To this end, data on the occurrence of melanoma within the drug development programs of marketed PD drugs was requested from the respective sponsors of the various therapies. Details on this request and subsequent data submissions are contained in Section 5.5.4 of this review.

5.2.2.2 AERS Data Review

An OPDRA Postmarketing Safety Review of anti-Parkinsonian agents associated with melanoma in the AERS database was conducted in May 2001. A total of 39 cases were identified (Sinemet-35, Requip-2, Eldepryl-1, and Permax-1). The report noted that the 35 Sinemet-related cases of melanoma were reported to the FDA over 25 years, a time period estimated to encompass well over 20 million prescriptions. The report concluded that the quality and quantity of melanoma cases within the AERS database did not support a clear relationship with Parkinson's disease therapy.

5.2.2.3 Epidemiology⁹⁵

Malignant melanoma involves cancerous changes to melanin producing cells found primarily on the skin. About 70% of melanomas appear on previously normal skin, and 30% occur in moles, nevi or other lesions.

Superficial spreading melanoma is the earliest form of melanoma. This represents 70% of the cases at the time of diagnosis. Nodular melanoma accounts for 15% of cases, and frequently presents as an ulceration that does not heal in adults 20 to 60 years of age. Acral lentiginous melanoma occurs in about 10% of the cases and generally appears on the palms, soles and mucosal surfaces in the elderly. Lentigo maligna melanoma occurs in 5% of the cases, generally in sun damaged skin of the head, neck, and arms in the elderly.

Melanoma accounts for 1 to 3% of all cancers within the United States, and about 5% of all skin cancers. Mortality due to melanoma is related to the depth of skin involvement. Superficial lesions <0.76 mm are virtually always curable with adequate excision, whereas lesions with depths >1.6 mm have only a 25% five-year survival rate.

⁹⁵ This epidemiology section was adapted from Dr. Prohaska's (DNDP) report of April 2001

FDA Table 55: Melanoma staging and prognosis from the American Joint Committee on Cancer, 2002

Stage	Thickness Range, mm (Breslow)	Five-year Survival (%)
0	In situ	>99.9
IA	Thickness 1 mm or less	95
IB	Thickness < 1mm, ulceration Thickness 1.01-2 mm	90
IIA	Thickness 1.01-2 mm, ulceration Thickness 2.01-4.0 mm	77 78
IIB	Thickness 2.01-4.0 mm, ulceration Thickness > 4.0 mm	63 67
IIC	Thickness > 4.0 mm, ulceration	45
IIIA	Any thickness, 1 node positive Any thickness, 2-3 nodes positive	70 63
IIIB	Any thickness, +/- ulceration 1-3 nodes positive	46-59
IIIC	Any thickness, +/- ulceration 1-4 nodes positive	24-29
IV	Distant metastases	6.7-18

The incidence of melanoma increases with age, with the peak age of incidence in the fourth decade. Under age 40, more women than men develop melanoma, whereas over age 40, men are more likely to develop melanoma.

Other risk factors for melanoma (as outlined by the sponsor) include: Caucasian race; light eyes; blond or red hair; family history (increases relative risk by two to eight time); personal history of melanoma or non-melanoma skin cancer; childhood sunburns; tendency to tan poorly; presence of atypical moles (dysplastic nevus) with irregular pigmentation and borders; presence of large number of ordinary melanocytic nevi (between 20-50% of melanomas develop in preexisting nevus.)

5.3 Sponsor Presentation of Data

5.3.1 Melanoma Case Characteristics

The sponsor states a total of 20 cases of malignant melanoma (in 19 patients) were identified during the rasagiline clinical development at the time of the NDA submission.⁹⁶ Fifteen (15) cases occurred in participants treated with rasagiline, one in a placebo-treated participant and three were diagnosed before treatment initiation.⁹⁷

The majority of cases (14) were diagnosed following the implementation of active skin examinations in all rasagiline clinical trials at the end of 2001. Teva notes that 11 of the

⁹⁶ Lock dates for data in the ISS of the NDA were September 3, 2002 (for studies 113 and 233), and May 2003 (for studies 123 and 135)

⁹⁷ It was unclear if the subjects identified with melanoma prior to treatment initiation were diagnosed before or after randomization.

15 rasagiline-treated cases were diagnosed in studies without a concurrent placebo group. The studies during which the cases were identified are detailed in Section 2.1 of this report.

Histologically, eight of the melanomas were invasive and twelve were in situ (NDA Appendix 18.3 pg. 2); of the 16⁹⁸ associated with rasagiline treatment seven were invasive and nine were in situ. The 15 rasagiline-treated participants with melanoma were exposed to rasagiline between 2.5 to 55 months (median 13 months, mean 21 months) prior to diagnosis.⁹⁹ Seven of the 15 cases were identified within nine months of treatment. Five of the rasagiline-treated cases were dosed at 2 mg/day, eight received 1 mg/day and two received 0.5 mg/day. Eleven cases (those from PRESTO and LARGO) had concomitant treatment with levodopa.

Only three of the 19 subjects with melanomas were participants in trials outside North America (NDA Appendix 18.3, Pg. 9). All melanomas occurred in white participants, with an average age of 67 years (range 47 to 75 years.)¹⁰⁰ One death had resulted from malignant melanoma at the time of the NDA submission.

A chart summarizing the characteristics of the melanoma cases is provided in Attachments 9.22 of this review.

5.3.2 Overview of Sponsor Position

Teva summarizes their primary assertions concerning the occurrence and analysis of melanoma cases during the rasagiline development program as follows:¹⁰¹

1. The relative increase in the melanoma cases seen in rasagiline trials compared to the SEER (Surveillance, Epidemiology, and End Results) cancer registry is due to both underreporting of overall melanoma cases to the SEER, and to the fact that SEER does not adequately capture in situ cases.
2. Some of the relative increase is due to a surveillance bias resulting from institution of screening for melanoma.
3. Some of the relative increase may also be due to an association between Parkinson's disease itself and melanoma, or confounders such as age, or smoking/socioeconomic status. The sponsor finds the case report literature suggesting a possible relation between levodopa therapy and melanoma unconvincing.
4. The higher rate of melanoma in North American subjects is consistent with this population having more melanoma risk factors than European subjects.

⁹⁸ As one subject had two melanomas (one invasive and one in situ), there were 16 cases of melanoma among the 15 rasagiline-treated subjects.

⁹⁹ Calculated by safety reviewer from sponsor Table 3, NDA appendix 18.3, pg. 24

¹⁰⁰ Calculated by safety reviewer from sponsor Table 3, NDA appendix 18.3, pg. 24

¹⁰¹ Rasagiline NDA, ISS Section 11.2

5. The latency of treatment with rasagiline is too short to support a causal association between the development of melanoma and rasagiline exposure.

5.4 Discussion of Specific Sponsor Concerns

Each of the sponsor's concerns summarized above (section 3.1) will be addressed in greater detail in the following sections (3.2.1-3.2.7) of this review.

5.4.1 Sponsor Concern: Incomplete Melanoma Ascertainment in SEER

5.4.1.1 SEER Introduction

According to its website (<http://www.seer.cancer.gov/>), the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute was founded in 1973, and currently collects data on cancer incidence and survival from 11 population-based and 3 supplemental registries. The registries (which include statewide registries in Connecticut, Hawaii, Iowa, New Mexico and Utah, in addition to metropolitan registries in Atlanta, Detroit, Los Angeles, San Francisco-Oakland, San Jose-Monterey, and Seattle) are estimated to encompass approximately 14 % of the United States population. In 2001, the SEER Program expanded coverage to include Kentucky and Greater California, while New Jersey and Louisiana resumed participation.

While cases of melanoma in situ are collected,¹⁰² SEER calculates melanoma rates for invasive lesions only. Although SEER employs stringent quality control measures and is recognized worldwide as a source of United States cancer statistics (<http://seer.cancer.gov/about/quality.html>), the sponsor notes that for melanoma in particular there are challenges to complete ascertainment.

SEER age-adjusted incidence of invasive melanoma for white males and females was 23.8 and 16.2 per 100,000, respectively, in 2000.¹⁰³

5.4.1.2 Overview of Sponsor Position on SEER

The sponsor raises the following considerations regarding the use of SEER in calculating melanoma background rates:

1. SEER does not have formal procedures to identify patients who are diagnosed with cancer outside of the registry system. The sponsor believes that less invasive melanomas can be managed in an outpatient setting, and evade reporting.

¹⁰² Zippin et al. Completeness of hospital cancer cases reporting from the SEER program of the National Cancer Institute. *Cancer* 1995;76:2343-50.

¹⁰³ (http://canques.seer.cancer.gov/cgi-bin/cq_submit?dir=seer2000&db=1&rpt=TAB&sel=^0^^49^2^^^0&x=SEER%20registry^0,1,2,3,4,5,6,7,8,9^Race^0,1,2&y=Sex^0,1,2^Statistic%20type^1,2,3&dec=4,4,4)

2. The extent of melanoma underreporting to SEER is likely to be substantial. Several studies estimating melanoma underreporting from between 10% to 21% are cited. (See Section 3.2.1.3 for references and details.)
3. Teva notes that while SEER does collect some data on melanoma in situ, it has not used the counts to compute in situ incidence rates. Teva states that presumably SEER is concerned about the completeness of its ascertainment (NDA Appendix 18.3, pg. 18).

5.4.1.3 Literature review of melanoma reporting to SEER

The following studies have addressed the topic of melanoma reporting to the SEER registry.

Reviewer comment: The following studies were cited by the sponsor in their detailed melanoma report within Appendix 18.3 of the rasagiline NDA. The study summaries below reflect the sponsor's descriptions of the research, although they have been heavily condensed by the writer of this review. Additionally, the information presented has been compared with the original studies by this reviewer for accuracy.

1. Zippen et al.¹⁰⁴ conducted a case-finding study of a sample of hospitals reporting to SEER in 1987, and found that 10 melanoma cases had been missed (3 of them in situ) among a total of 149 missed cancer cases.
2. In a study by Koh et al.,¹⁰⁵ an independent tabulation of incidence estimated that between 12% and 18% of new melanoma cases were not recorded in the Massachusetts cancer registry for the period between 1982 and 1986.
3. In western Washington state, researchers found a trend of increasing melanoma underreporting to a local registry, ranging from 2% in 1974 to 21% in 1984.¹⁰⁶
4. A study¹⁰⁷ in northern California attempted to ascertain how many melanoma cases were diagnosed solely in a private physician's offices, dermatology clinics, or dermatopathology offices. An increasing trend in melanoma underreporting to SEER was observed, rising from 4% in 1973 to 16% in 1985, with a larger number of in situ cases being missed.

¹⁰⁴ Zippen et al. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. *Cancer* 1995;76(11):2343-50.

¹⁰⁵ Koh et al. Systematic underreporting of cutaneous malignant melanoma in Massachusetts. Possible implications for national incidence. *J Am Acad Dermatol* 1991;24(4): 545-50.

¹⁰⁶ Karagas MR. The effects of changes in health care delivery on the reported incidence of cutaneous melanoma in western Washington States. *Am J Epi* 1991; 133(1):58-62.

¹⁰⁷ Seiffert J. Underreporting of melanoma. *J Natl Cancer Inst* 1992;84:289.

5. In a survey of dermatologists conducted in Iowa,¹⁰⁸ underreporting to the SEER state cancer registry was estimated to be between 10.4% and 17.1% for the period of 1977 to 1994. The authors of this study concluded that the underreporting in Iowa was consistent with that in Massachusetts (at least 12% and perhaps as great as 18%), Connecticut (16% of melanomas in Connecticut residents were diagnosed in out-of-state laboratories),¹⁰⁹ Western Washington State (21%), and in Northern California (16% underreporting of in situ lesions.)
6. To assess the completeness of melanoma reporting, age-adjusted average annual incidence rates were calculated for two registry systems within the North American Association of Cancer Registries: the National Program for Cancer Registries [NPCR] and SEER.¹¹⁰ This study is notable in that the SEER data was used as the “gold standard” comparator, as it was considered to have the higher rate of case ascertainment.

For both SEER and the NPCR, reporting increased over the time (rates for 1995-1997 were compared to 1992-1994). However, rates increased considerably more for NPCR (93%) than for SEER (32%).

The authors concluded that the greater increase in incident rates reported by NPC, as compared to SEER, registries is likely due to improved case ascertainment over time. They acknowledge that underreporting to SEER may also occur, but apparently to a lesser degree. It is noted that ascertainment of melanoma cases is especially likely to be incomplete for early stage cancers diagnosed and treated at physician offices, which, unlike hospitals, do not routinely report cases to the central cancer registries. Underreporting of localized early invasive disease is of greater concern than underreporting of in situ cases, as generally only invasive cases are included in the calculation of incidence rates.

Reviewer comment: *Early invasive melanomas have high 5-year survival rates (for example, 95% for Stage IA and 90% for Stage IB) following treatments such as wide local excision, which may be performed as an outpatient. The sponsor maintains that SEER does not adequately capture in situ and early melanomas which are either treated as outpatients or diagnosed in pathology laboratories which are not affiliated with a registry hospital.*

To clarify the case reporting methods within SEER and ascertain whether early melanomas treated on an outpatient basis would be captured, I collected samples of policies on case collection from the various SEER component registry websites. These are provided in Appendix 5.2 of this review. In addition, I contacted staff at the central

¹⁰⁸ Merlino et al. The independent pathology laboratory as a reporting source for cutaneous melanoma incidence in Iowa, 1977-1994. *J Am Acad Dermatol* 1997;37(4):578-85.

¹⁰⁹ Bologna et al. Histologic evaluation of pigmented lesions in Connecticut and its influence on the reporting of melanoma. *J Am Acad Dermatol* 1992;26:198-202.

¹¹⁰ Hall et al. The reporting of cutaneous melanoma to cancer registries in the United States. *J Am Acad Dermatol* 2002;49:624-30.

SEER registry and at the component registries by e-mail, asking whether in situ and early melanomas treated on an outpatient basis would be captured by the registry. These sources indicated that information on melanomas is collected from private laboratory facilities as well as hospitals, and that active measures are taken to gather cases from outpatient practitioners. One source stated that for her component registry she believed essentially all cases of melanoma would be registered eventually, although in situ and early melanomas would not be registered as promptly.

In addition to the above studies, the sponsor presents the following two studies as demonstrations of potentially incomplete melanoma ascertainment within SEER:

1. The sponsor states that concern of increased melanoma rates following psoralen/ultraviolet A (PUVA) treatment for psoriasis was raised by a series of case reports, prompting a prospective cohort study (by Stern et al.¹¹¹) of 1380 patients exposed to PUVA (Teva melanoma report, June 2001, pg. 13). From 1975 to 1990, no increase in melanoma incidence was observed (melanoma in situ was excluded from the analysis.) In the period from 1991 to 1996, however, a relative risk of 5.4 (95% CI: 2.2 to 11.1) was found compared to SEER rates.

In a letter to the editor in response to the Stern study, Whitmore et al.¹¹² questioned the validity of using SEER as an external control. They noted that SEER data may underestimate true melanoma incidence, as “melanoma is frequently excised in doctors’ offices and specimens may be sent to distant laboratories.” In addition, Whitmore referenced a 1992 survey of the American Academy of Dermatology members in which the incidence of melanoma and melanoma in situ was double the incidence of invasive melanoma in SEER. In the response by Stern, however, several limitations of the survey were noted, including a 35% response rate and questions that relied on practitioners’ recollections of melanoma over the previous decade.

2. In a large cancer incidence study of male US Air Force officers,¹¹³ aviators were found to have an elevated melanoma risk when compared to SEER (Standardized Incidence Ratio [SIR] 1.5, 95% CI: 1.00 to 2.14.) However, when aviators were compared to non-flyers, no greater melanoma risk was seen (SIR 1.15; 95% CI: 0.75 to 1.78). Although it was unclear from the description of the analytic methods, it appeared that both non-aviators and aviators had increased melanoma rates compared to SEER.

Teva suggests underreporting to SEER as one explanation for finding of increased risk when aviators are compared to SEER rates, but no increased risk when aviators were compared to non-aviators (Teva Melanoma Report June 2001, pg. 12).

¹¹¹ Stern et al. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). N Eng J Med 1997;336:1041-5.

¹¹² Whitmore SE, Morison WL. Melanoma after PUVA therapy for psoriasis. N Eng J Med 1997;337(7):502-3.

¹¹³ Grayson JK. Cancer incidence in United States air force aircrew, 1975-89. Aviat Space Environ Med 1996;67:101-4.

Limitations of the study included the older time period examined (from 1975 to 1989), and that information on melanoma was taken from hospital discharge records, which may not have included outpatient procedures.

5.4.1.4 Sponsor's study of invasive and in situ melanoma

Teva also presents data from an investigation conducted by their consultant, Dr. Darrell Rigel, to assess the prevalence of invasive versus in situ melanoma.¹¹⁴ In the introduction of the study, the author states that while the ratio of invasive to in situ melanomas is unknown, recent estimates from SEER suggest a predominance (61%) of invasive lesions (in contrast to the majority of in situ cases found during rasagiline development.)

In the sponsor-supported study, data was collected retrospectively from five U.S. metropolitan area dermatopathology laboratories on all melanoma lesions submitted in 2000 and 2001. Duplicate lesions (from initial and definitive excisions) were eliminated. A total of 9,143 melanoma cases were evaluated, of which 5189 (57%) were in situ and 3954 (43%) invasive. Dr. Rigel notes this is the reverse of the SEER ratio and again stresses that SEER may significantly underestimate the population prevalence of melanoma, especially in situ melanoma, due to failure to register outpatient treatment.

5.4.1.5 Additional Sponsor Concern regarding SEER

The sponsor reports that the American Association of Central Cancer Registries (AACCR), an organization that includes all the SEER registries, has questioned whether the trend away from hospitalization has lead to cancer underreporting in general. However, melanomas were not included among the cancers audited in the study the AACCR made commentary on (June 2001 Teva melanoma report).

Reviewer Comment: There is considerable evidence for underreporting of melanomas to SEER, especially in situ cases. However, estimates on SEER case ascertainment from the literature suggest that a maximum of approximately 20% of cases may be missed. Thus, for invasive melanomas, the SEER database (with or without adjustment for potential underreporting) remains one of the appropriate comparison groups in evaluating the occurrence of melanoma within the rasagiline development program, although other comparison groups may better address confounders such as Parkinson's disease or melanoma screening.

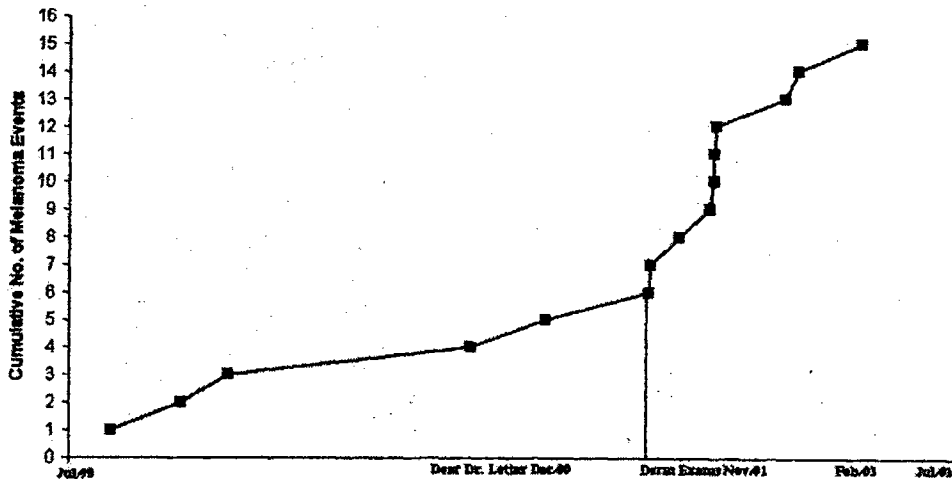
5.4.2 Sponsor Concern: Surveillance Bias following Screening

Teva asserts that the institution of a melanoma screening program likely resulted in a surveillance bias. The sponsor includes the following figure as an illustration of the increase in case accumulation following active screening:

¹¹⁴ Malignant Melanoma: Evaluation of mix of in situ versus invasive lesions with pathology laboratory confirmation," submitted as ISS Appendix 18.3, Attachment 5, within the Rasagiline NDA. Prepared by Dr. Darrell Rigel

FDA Figure 3: Rate of Melanoma Cases Before and After Active Skin Examinations

Figure 1. Number of melanoma cases before and after active skin examinations



* Additional 4 melanoma events were identified before treatment initiation or on placebo between Nov/01 and Oct/02

Reviewer Comment: The occurrence of a surveillance bias secondary to active screening is addressed in the FDA analysis via comparison with a screened population (calculated from age-specific rates from within the American Academy of Dermatology melanoma screening study) in Section 5.3.3 below.

5.4.3 Sponsor Concern: Confounding by Melanoma Risk Factors

Teva notes that most (17 of 20, or 85%) cases of melanoma occurred in North American participants (16 of the 17 North American cases were treated with rasagiline; the remaining melanoma case was identified prior to treatment.) The sponsor hypothesizes that differing phenotypic characteristics and geographic risk factors may account for this difference in melanoma rates between North American and non-North American (Israel/Europe/Argentina) subjects.

Reviewer comment: The sponsor theorizes that variations in melanoma rates between trials with sites either within or outside North American reflect the background melanoma rates in the different locations. However, no melanoma background rates by country were presented by the sponsor. I compiled a chart displaying the age-adjusted melanoma rates for the various geographic locations of the clinical sites, which is presented in the Attachments 9.25 of this review.

Overall, background rates of melanoma were indeed higher in North America and particularly the United States (range of 16.6 – 24.4 per 100,000 for men, 9.9 – 13.4 per 100,000 for women) than in the Non-North American countries in which LARGO was conducted (range 2.3 – 12.4 per 100,000 for men, 3.3 to 15.6 for women). The rates were

even lower for Argentina (1.2 per 100,000 for men, 2.3 per 100,000 for women), although Argentina was the only location for which the reference (detailed in Attachment 9.25 of this review) stated that data may be incomplete as evidenced by quality indicators or due to the conditions in which the registry operates.

The sponsor provided the following table as an illustration that subjects in North American trials (PRESTO/133 and TEMPO extension/233) have a higher proportion of non-melanoma skin conditions in addition to a greater number of melanomas than the Europe/Israel/Argentina trial (LARGO/122). They note that non-melanoma skin cancers share common risk factors with melanoma (NDA Appendix 18.3, pg 28).

FDA Table 56: Biopsy Results from Skin Screening Per Total Participants in the Three Phase III Clinical Trials (Sponsor ISS Appendix 18.3 Table 4)

Table 4. Biopsy results of patients undergoing skin examinations

Diagnosis	Study 133/135 N=472		Study 122/123 N=687		Study 233 N=306	
	N	%	N	%	N	%
In situ melanoma	5	1.1	1	0.1	4	1.3
Invasive melanoma	3	0.6	1	0.1	3	1.0
Basal cell carcinoma	23	4.9	6	0.9	9	2.9
Actinic keratosis	14	3.0	4	0.6	4	1.3
Squamous cell carcinoma	9	1.9	1	0.1	4	1.3
Melanocytic nevus including simple lentigo	59	12.5	30	4.4	36	11.8
Non melanocytic pigmented lesion	31	6.6	9	1.3	22	7.2
Other skin lesion	20	4.2	8	1.2	16	5.2

Reviewer comment: The “N” in the above table represents the total number of participants in the respective trials. As not all participants underwent dermatologic screening, it is uncertain if the total subjects in each trial is the appropriate denominator for the percentage calculations.

I re-calculated the table below using the number of subjects from each trial who filled out melanoma risk factor (MRF) profiles, as taken from the MRF datasets provided by the sponsor. These files are described further in Attachments 9.27 of this review. I utilized the number of subjects from each trial providing information on their melanoma risk factors as a surrogate for being in the trial at the time when subjects were undergoing skin examinations, and hence were likely to have been screened for melanoma.

FDA Table 57: Biopsy Results from Skin Screening per Participants completing Melanoma Risk Factor Forms in the Three Phase III Clinical Trials (Sponsor ISS Appendix 18.3 Table 4)

Diagnosis	PRESTO Study 133/135 N=346		LARGO Study 122/123 N=471		TEMPO Ext. Study 233 N=233	
	N	%	N	%	N	%
In situ melanoma	5	1.4	1	0.2	4	1.7
Invasive melanoma	3	1.0	1	0.2	3	1.3
Basal cell carcinoma	23	6.6	6	1.2	9	3.8
Actinic keratosis	14	4.0	4	0.8	4	1.7
Squamous cell carcinoma	9	2.6	1	0.2	4	1.7
Melanocytic nevus including simple lentigo	59	17.5	30	6.4	36	15.4
Non melanocytic pigmented lesion	31	8.9	9	1.9	22	9.4
Other skin lesion	20	5.7	8	1.7	16	6.8

The re-calculated table above continues to demonstrate similar risks for the two North American studies, PRESTO and TEMPO, even though the study populations differed in that one was receiving concomitant levodopa therapy and the other was not. The two North American studies also continue to have a considerably higher melanoma risk than the non-North American study LARGO.

Teva further assessed melanoma risk factors directly through use of a Melanoma Risk Factor (MRF) form, which was completed by 1251 participants. The sponsor concludes from the following table that risk factor profiles were similar for the two North American studies (PRESTO/133 and TEMPO/233), and increased in comparison to the LARGO/122 (Europe/Argentina/Israel) study.*

FDA Table 58: Melanoma Risk Factor Profile among Participants of the three Principle Trials (of those filling out the MRF form) (Sponsor ISS Appendix 18.3 Table 6)

Table 6. The percent of patients having multiple risk factors

Accumulated no. of MRF	Study 133/135 (% of patients)	Study 122/123 (% of patients)	Study 233 (% of patients)
≥ 3	51.7%	25.5%	54%
≥ 4	38.2%	15.9%	33.6%
≥ 5	20.8%	9.1%	20%

* The TEMPO core study, TVP-1012/232, had already been completed by the time subjects were asked to complete the MRF forms. Teva states that approximately 10% of the TEMPO core patients were contacted and gave their consent to fill the melanoma risk factor questionnaire. In the table above, data is presented for the TEMPO Extension study 233, but not for the TEMPO core study 232.

Reviewer Comment: *Teva also presents information that rasagiline-treated subjects had more melanoma risk factors at baseline than placebo-treated subjects (for instance, for suspicious lesions at baseline in study 133 [PRESTO]) (NDA Appendix 18.3, pg. 27). As also noted by a previous FDA reviewer,¹¹⁵ in a randomized controlled trial risk factors should have been distributed equally between placebo and treatment arms. Likewise, emphasizing differences in specific risk factors between groups raises the concern of multiple comparisons, as there are a sizable number of melanoma risk factors, many of which may occur commonly in the general population. These factors make possible differences in risk factor profiles between groups a lesser consideration in assessing whether the occurrence of melanomas during the rasagiline development program is more than one would expect.*

5.4.3 Sponsor Concern: Confounding by Medications or Parkinson's disease

5.4.3.1 Confounding by Parkinson's disease

5.4.3.1.1 Sponsor's Hypotheses on Melanoma and PD

Teva's report proposes that the possible link between Parkinson's disease and melanoma may be due to a third factor, such as increasing age or a common genetic predisposition. The sponsor summarizes a proposed pathophysiological pathway that may link melanoma and PD (ISS Appendix 18.3, Section 7.6.2). It is also suggested that higher socioeconomic status (which is associated with melanoma), may also be associated with Parkinson's disease through an inverse relationship with smoking (ISS Appendix 18.3, pg. 3).

Reviewer comment: *There is support in the literature, from both retrospective and prospective studies, of an inverse relationship between smoking and Parkinson's disease.¹¹⁶ There is also evidence of an inverse association between PD and coffee and/or alcohol consumption.¹¹⁷*

5.4.3.1.2 Sponsor-initiated studies on PD and melanoma

The sponsor initiated the following two cohort studies (in Israel and North America) to assess the occurrence of melanoma among PD patients:

¹¹⁵ Review and Evaluation of Clinical Data for Malignant Melanoma in the Rasagiline Clinical Development Program, dated 9/21/2001. Prepared by Dr. David Gan, FDA/CDER/DNDP

¹¹⁶ Hernan et al. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann Neurol* 2001;50(6):780-6.

¹¹⁷ Ragonese et al. A case-control study on cigarette, alcohol, and coffee consumption preceding Parkinson's disease. *Neuroepidemiology* 2003;22(5):297-304.

1. EP001: Screening for Melanoma in Israeli PD patients¹¹⁸

The sponsor states the purpose of this study was to assess the frequency and characteristics of skin cancers among PD patients, at all stages of the disease and treated with any anti-Parkinson's therapy (except rasagiline). An ongoing cohort is being assembled through referrals from treating neurologists at nine medical centers in Israel, and consenting participants are sent for dermatologic screening. Information on PD treatment and melanoma risk factors are collected.

As of July 2003, Teva reports that 1207 PD patients had been evaluated by a dermatologist, and data for 1146 were available for interim analysis. Suspicious pigmented lesions were found in 6.1% of subjects. Eight cases of melanoma (0.7% of those screened) had been identified, of which seven were in situ and one invasive. The authors note that this prevalence is about ten times higher than background rates estimated from the general Israeli population for the period of 1996-2000.

2. EP002: US and Canada Cohort Study of Malignant Melanoma in Individuals with Confirmed Parkinson's Disease¹¹⁹

This cohort is being drawn from 31 North American medical centers, some of which also participated in the rasagiline development trial. The study design is similar to the Israeli cohort described above.

Teva reports that interim results show a melanoma rate of 1 in 143 (or 0.7%, from the Israeli cohort) and 1 in 76 (or 1.3%, from the North American cohort), with a in situ/invasive ratio of 7:1 and 14:4, respectively. This rate was found to be higher than the prevalence found in similar (screening) cohort studies conducted in the general population (1 in 770 [0.13%] to 1 in 60 [1.7%].)^{120 121}

In addition to assessing whether there may be an increased risk of melanoma in PD patients, the sponsor also approached the topic from the reverse perspective: whether there is an increased risk of PD in persons with a previous history of melanoma. The sponsor initiated a study¹²² which enrolled 919 melanoma patients from 10 clinical sites in the United States. Patients were evaluated for a personal and family history of PD, and the prevalence of PD was compared to national estimates via a Poisson distribution.

¹¹⁸ ISS Appendix 18.3, Section 7.3.1

¹¹⁹ ISS Appendix 18.3, Section 7.3.2

¹²⁰ Koh et al. Evaluation of melanoma/skin cancer screening in Massachusetts. *Cancer* 1990;65:375-9.

¹²¹ Carli et al. Skin cancer day in Italy: method of referral to open access clinics and tumor prevalence in the examined population. *Eur J Dermatol* 2003;13:76-9.

¹²² Malignant melanoma: evaluation of association of Parkinson's disease in patients with history of melanoma, submitted as ISS Appendix 18.3, Attachment 4, within the rasagiline NDA. Prepared by Dr. Darrell Rigel

For subjects over age 60, 26 (6.7%) had PD, which the sponsor compared to a background PD prevalence of 1% (based on a study in Scandinavia.) Teva states that to further validate the study a control group of 862 age-gender matched controls was assembled, which was then compared to 862 (of the original 919) melanoma cases. Parkinson's disease was noted in 1.3% of controls, versus 2.9% in those with a history of melanoma.

Reviewer comment: The presentation of this study within the NDA lacked details on a number of factors (including participant selection) important in evaluating the research.

5.4.3.2 Confounding by other medications

The sponsor listed other medications with possible associations with melanoma, including levodopa, photosensitizing drugs, psoriasis treatment with oral psoralen and ultraviolet A radiation (PUVA) and immunosuppressive drugs.

For levodopa, the sponsor states that although there have been a number of case reports suggesting a possible association between levodopa and melanoma, they believe it is more reasonable to conclude that the association is between PD and melanoma, rather than between levodopa and melanoma (ISS Section 11.2). Teva offers a hypothesis as to the underlying basis for this possible association, as described in Section 5.4.3.1.1 of this review.

5.4.3.2.1 Literature discussion of levodopa and melanoma

Beginning with a report by Skibba et al. in 1972,¹²³ approximately 50 case reports of melanomas occurring in Parkinson's disease patients treated with levodopa have been reported in the literature (NDA Appendix 18.3, pg. 16). A summary of these case reports and their references is provided in Attachment 9.24 of this review.

Based in part on such reports, the labeling for carbidopa-levodopa carries the following contraindication: "Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma." (Physician's Desk Reference)

Beyond the case reports and series, relatively few studies have investigated the relationship between levodopa, Parkinson's disease and melanoma. No cohort-based study specifically addressing the contribution of levodopa therapy to the development of melanoma in PD patients has been performed. One study attempted to address the issue by prospectively asking 1,099 patients at a melanoma clinic if they had been taking levodopa.¹²⁴ As only one had, the authors concluded that if levodopa was a factor in melanoma development, it was not a significant one.

¹²³ Skibba et al. Multiple primary melanoma following administration of levodopa. Arch Pathology 1972;93:332-6.

¹²⁴ Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. JAMA 1978;240:554-5

While such studies do not provide information on levodopa treatment, several studies on cancer in Parkinson's disease patients provide information on melanoma in this population. In general, studies of cancer incidence or mortality in Parkinson's disease patients have documented lower overall cancer rates than in the general population, and especially for smoking-related cancers.^{125 126 127} A few studies, despite finding lower overall cancer rates, have noted a higher than expected occurrence of melanoma. These include the following two studies:

1. Jansson and Jankovic¹²⁸ utilized a retrospective examination of more than 400 medical charts to examine cancer rates in persons with Parkinson's disease. A relatively low overall cancer rate was observed (relative risk ~0.3), with the exception of thyroid cancer and melanoma. An elevated rate of melanoma was noted, however; with two cases observed compared to 0.3 cases expected ($p = 0.04$). (NDA Appendix 18.3, pg. 32)
2. Moller et al.¹²⁹ also studied cancer among Danish PD patients. A cohort of 7046 PD patients treated as inpatients between 1977 and 1989 was identified via a registry of hospital admission records. Information on cancer incidence and deaths among cohort members until the end of 1990 was obtained from the Danish cancer and death registries. Relative risks were calculated as the ratios of the observed to the expected (based on cancer incidence in the general Danish population) number of cases of cancer.

While a lower than expected risk was observed for overall cancer (relative risk 0.88; 95% CI: 0.8-1.0) and especially for smoking-related cancers (0.49; 95% CI: 0.4-0.6), there was a significantly increased relative risk for skin melanoma (1.96; 95% CI: 1.1-3.2) and for malignancies of unknown origin (1.76; 95% CI: 1.2-2.5).

Teva commissioned a continuation of the study by Moller, extending follow-up through 1998.¹³⁰ Persons who were not Danish citizens, who died during hospitalization, or were under age 20 at diagnosis were excluded, resulting in a cohort of 14,031 subjects for cancer risk analyses.

The authors state that in principle the Danish Cancer registry should contain cases of invasive melanoma only. However, when researchers audited melanoma reports for both

¹²⁵ Beau-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with Parkinsonism: possible clues to aetiology? *J Neurool Neurosurg Psychiatry* 1995;58:293-9.

¹²⁶ Hoehn MM, Yahr JG. Parkinsonism: onset, progression, and mortality. *Neurology (Minneap)* 1967;17:427-42.

¹²⁷ Vanacore N et al. Mortality cancer risk in parkinsonian patients: a population-based study. *Neurology* 1999;52:395-8.

¹²⁸ Jansson B, Jankovic J. Low cancer rates among patient with Parkinson's disease. *Ann Neurol* 1985;17:505-9.

¹²⁹ Moller et al. Occurrence of different cancers in patients with Parkinson's disease. *BMJ* 1995;310:1500-1.

¹³⁰ Cancer incidence among patients with Parkinson's disease: a nationwide cohort study in Denmark, internal report prepared by _____ (Rasagiline NDA, ISS Appendix 18.3, pg. 86/Attachment 3.)

cohort members and a sample of non-PD melanoma cases, they found that in only 64% and 67% (respectively) was a clear statement of invasiveness present.

Overall, 1196 cancers were found in the Parkinson's disease cohort, yielding a standardized incidence ratio (SIR) compared to age and sex-specific rates for the general population of 0.87 (95% CI:0.82-0.92). Similar to previous studies of cancer in PD patients, the primary decrease was seen in smoking-related cancers. An elevated incidence was observed for melanoma (SIR 2.04, 95% CI: 1.5-2.8) and non-melanoma skin cancers (SIR 1.24;1.1-1.4). For melanoma, 42 cases were documented for the cohort, which included 66,163 person-years of follow-up.

5.4.4 Sponsor Concern: Increasing Melanoma Rates Worldwide

Teva notes that melanoma rates are rising faster than for any other cancer worldwide (ISS Section 11.2), and the incidence in the United States has increased by more than 3% annually since 1981.¹³¹ ¹³² In 1990, the Centers for Disease Control (CDC) estimated that 1 person in 105 would develop melanoma during their lifetime, compared to 1 in 75 in 2000, and 1 in 50 by 2010 (NDA Appendix 18.3, pg. 13). The SEER registry has also reflected this increase. This is demonstrated in a study by Hall et al.,¹³³ which reviewed SEER incidence data from 1973 to 1994, and found an increase in invasive melanoma incidence of about 150% in white males and about 90% in white females.

Teva further notes that dysplastic nevi can be difficult to distinguish from melanoma in situ, and may be misclassified as such.

Reviewer comment: *Although there is some discussion in the literature on the causality behind the rising melanoma rates (including overdiagnosis versus a true increase in incidence)¹³⁴, the rate increase both within the United States and worldwide is well documented. This factor will be addressed in the analysis of melanoma within the rasagiline trials by selecting a comparator group as closely temporally matched to the time periods covered by the rasagiline studies as possible.*

5.4.5 Sponsor Concern: Insufficient Latency

The sponsor finds the timing between exposure to rasagiline and the identification of melanoma to be too short for biological plausibility. For example, the sponsor sites Patient 164 (rasagiline 2 mg/day), who was stated to have had a suspicious lesion on his forehead for approximately a year. This was confirmed as an invasive melanoma (Clark's level IV) two and half months after the patient entered trial TVP-1012/232. The

¹³¹ Goldstein BG, Goldstein AO. Diagnosis and management of malignant melanoma. Am Fam Physician 2001;63:1359-68

¹³² <http://healthlink.mcw.edu/article/960318399.html>

¹³³ Hall et al. Update on the incidence and mortality from melanoma in the United States. J Am Acad Dermatol 1999;40:34-42.

¹³⁴ Burton RC, Armstrong BK. Current melanoma epidemic: an nonmetastasizing forma of melanoma? World J surg 1995;19(3):330-3.

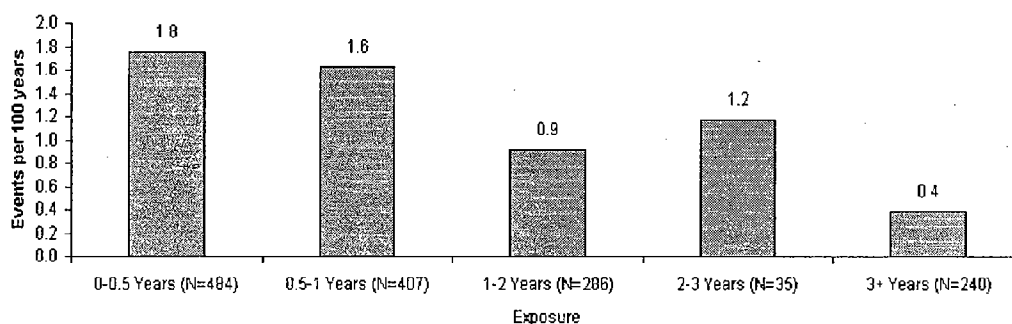
sponsor commented that given the advanced state of the disease “it was nearly inconceivable that it was the drug induced the melanoma or drove tumor progression in so short [sic] time.”(Teva melanoma report June 2001, pg. 17).

From sponsor Table 3 (Appendix 18.3, pg. 24), the 15 rasagiline-treated participants with melanoma were exposed to rasagiline between 2.5 and 55 months (median 13 months, mean 21 months) prior to diagnosis.

The sponsor provides the following figure, depicting the number of melanomas (both in situ and invasive) per 100 patients, and concludes that there is no increase with duration of treatment.

FDA Figure 4: Melanoma per 100 Patient-Years by Duration of Rasagiline Exposure (Sponsor ISS Appendix 18.3 Figure 2)

Figure 2. Melanoma cases per 100 patients years of exposure



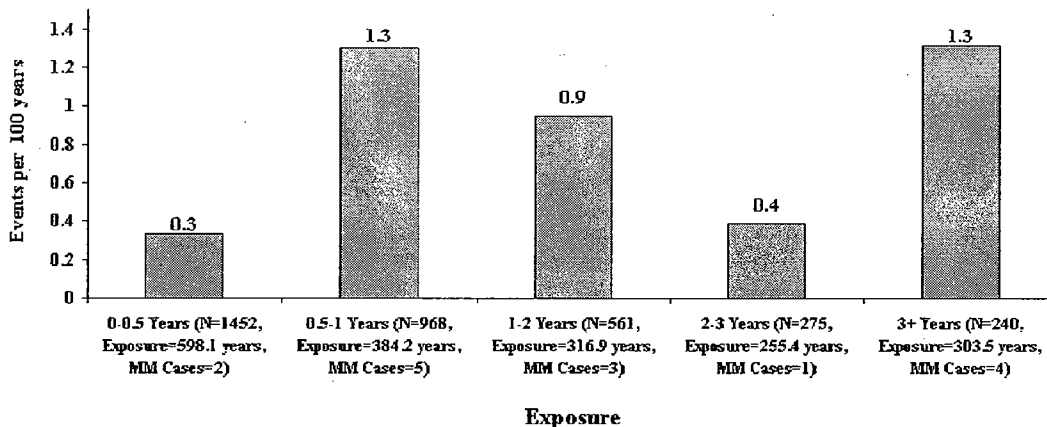
Reviewer Comment: The sponsor was contacted to clarify how the figure above was constructed: whether subjects were assigned to the time period corresponding to their full exposure duration, or whether their exposure time was allotted to each time period to which they contributed data. The sponsor confirmed¹³⁵ that the first method was used, wherein each subject’s exposure was counted only in the time period corresponding to their full exposure duration.

For the entire time a patient is exposed to a drug, he or she has the opportunity to develop an AE (in this case, melanoma). Thus the appropriate way to do this analysis is to include the exposure a patient contributes to each duration strata. For example, a patient who remains in the study for 1.5 years would contribute 0.5 years to the first six month strata, 0.5 years to the second six month strata, and 0.5 years to the 1-2 year strata. At the request of the FDA the sponsor repeated the above analysis using the correct method of attributing exposure time.

¹³⁵ E-mail correspondence received May 10, 2004.

FDA Figure 5: Melanoma per 100 Patient-Years by Duration of Rasagiline Exposure (Revised)

Figure 2. Melanoma Events (in-situ and invasive) per 100 Subject Years by Exposure Categories in Rasagiline Clinical Trials
(Patients assigned to time period they contributed to it exposure time)



The corrected figure does not demonstrate the generally inverse relationship between melanoma and treatment duration noted in the initial figure. The pattern of melanoma rates over time shown in the corrected figure above appears random and does not lend itself to easy interpretation.

As a clarification, the sponsor states that neither of the figures included cases that were identified prior to treatment initiation.

5.4.6 Sponsor Concern: Differential Exposure to Rasagiline versus Placebo

The sponsor states that although most cases of melanoma were observed in persons treated with rasagiline, this is reflective of the higher proportion of participants assigned to rasagiline versus placebo treatment in the North American studies. Teva notes that in U.S. active treatment studies, exposure to rasagiline (1457 patient-years) was more than 10-fold higher than exposure to placebo (137 patient-years) (NDA Appendix 18.3, pg. 31).

Teva further states that most of the exposure to rasagiline is derived from active treatment studies without a placebo group, precluding direct comparison.

5.5 Ongoing FDA Review

5.5.1 Comparison Group Overview

A number of confounding factors complicate the analysis of melanoma within the rasagiline development program, including concomitant Parkinson's disease, dermatologic screening, other medications (especially levodopa), variable geographic location/melanoma risk factors and the rapidly increasing rates of melanoma worldwide.

Several possible comparison groups are available for the analysis, each with its particular strengths and limitations in addressing the various confounding factors listed above. These comparison groups are listed in the table below.

FDA Table 59: Potential Comparison Groups for the Analysis of Melanoma within the Rasagiline Development Program

Comparison Group	Most Suitable for Evaluating...
SEER	Invasive melanoma within in a United States population
Other PD therapy datasets	Concomitant PD, levodopa therapy, and participation in a clinical trial
American Academy of Dermatology Screening Program data	Screened populations within the United States; In situ melanomas

5.5.2 SEER Data as the Comparator Group

The following table compares the observed seven invasive cases of melanoma that had occurred among rasagiline-treated, North American subjects¹³⁶ at the time of the NDA submission to the expected rates, as calculated by age-specific rates from the SEER cancer registry. The SEER expected rates utilized were those from the sponsor analysis for the initial two invasive cancers (at the time of the June 2001 report shown above [Section 5.2.2.1.1] of this review), but were adjusted for the additional person-year exposures to rasagiline (2030 person-years total)¹³⁷ compared to the first analysis (882 person-years).¹³⁸ This adjustment assumes the age and gender profile of the overall subjects the time of the 120 Day Safety update (December 2003) was similar to that at the time of the initial sponsor calculation of expected cases (June 2001). Confidence intervals were calculated via the same Poisson method utilized by the sponsor for this previous (June 2001) SEER comparison table.¹³⁹ Comparisons are also shown for one and a half, two and three times the expected rates from SEER, as a correction for possible underreporting.

¹³⁶ The seven invasive cases included in this analysis were:

¹³⁷ NDA 120 Day Safety Update, Section 2.1.1

¹³⁸ Prior FDA Review: Malignant Melanoma in the Rasagiline Development Program. Prepared by Dr. David Gan, Dated 9/21/2001.

¹³⁹ The method used is described in the following reference: Liddell FDK. Simple exact analysis of the standardized mortality ratio.

FDA Table 60: Comparison of Observed Invasive Melanoma Cases to the Expected Melanomas Cases as Per SEER Melanoma Rates for the General Population (Adjusted up to Three-Fold for Potential Under-Reporting)

Observed/Expected Analysis using SEER Rates		
7 Invasive Cases Observed (NDA Submission – Sept. 2003)		
Expected Number of Melanomas as per SEER rates	Obs/Exp Ratio	95% CI
0.9 cases (1 x SEER)	7.8	3.1, 16.0
1.3 cases (1.5 x SEER)	6.2	2.2, 11.1
1.8 cases (2 x SEER)	3.9	1.6, 8.0
2.7 cases (3 x SEER)	2.6	1.04, 5.3

***Reviewer comment:** The table above demonstrates that the number of melanomas within the rasagiline development program was more than would be expected based upon the rate of melanoma in the general population, as reported to SEER. This is true even when the analysis is restricted to invasive melanomas (for which the reporting to SEER is considered more accurate) and possible under-reporting to the SEER database is corrected by a factor of two- and three-fold. However, SEER reflects melanoma in the general population, while participants in the melanoma development program were actively screened for melanoma.*

5.5.3 AAD Screening Data as Comparator Group

Melanoma incidence data was requested from the American Academy of Dermatology (AAD) screening program, which performed voluntary screening of community members who were solicited through public service announcements in the local media. This population was selected as a comparison group specifically to address the effect of active screening in the rasagiline development program. An additional advantage of this comparison group is that it sought to gather pathologic confirmation on all suspicious lesions identified by screening. This would greatly reduce the potential bias toward invasive melanomas, which may be better captured by cancer registries due to their more extensive treatment. Limitations of the AAD screening data as a comparison group include that these are general population members (who likely do not have Parkinson’s disease and were not exposed to other PD therapies), and that persons who responded to community advertising for screening may have considered themselves at higher risk or have concerns about a specific lesion (leading to an inflated rate of melanoma, even for a screened population). The age-stratified rates of both invasive and in situ melanoma for 242,374 men and women screened in the AAD screening program are provided in Appendix 9.28 of this review.

The expected number of melanoma cases for the rasagiline development program was calculated by applying age specific incidence rates by gender to the patient profile in the Melanoma Risk Factor (MRF) files supplied by Teva (described further in Attachments 9.27 of this review). All participants within the file were included, and the population

was *not* restricted to Caucasian subjects only. This was done because the members within the file were primarily Caucasian (96%) in any case, and although the reference group was not restricted to Caucasians only, it also was primarily so (95%). Based upon these calculations, expected rates follow in the table below:

FDA Table 61: Calculation of Expected Melanomas for Men in the Rasagiline Development Program Using Melanoma Rates from the American Academy of Dermatology Screening Program

Age Group	Invasive Melanoma			In Situ Melanoma		
	# of Pts.*	AAD Rate per 100,000	Expected as per AAD	# of Pts.*	AAD Rate per 100,000	Expected as per AAD
<45	24	71.6	0.017	24	22.6	0.005
45-54	97	176.2	0.171	97	79.0	0.077
55-64	229	170.4	0.390	229	70.2	0.161
65-74	238	205.5	0.489	238	79.0	0.188
75+	73	167.5	0.122	73	51.5	0.038
Total	661		1.19	661		0.469

*Number of rasagiline participants from the MRF file by gender and age category

FDA Table 62: Calculation of Expected Melanomas for Women in the Rasagiline Development Program Using Melanoma Rates from the American Academy of Dermatology Screening Program

Age Group	Invasive Melanoma			In Situ Melanoma		
	# of Pts.*	AAD Rate per 100,000*	Expected as per AAD	# of Pts.*	AAD Rate per 100,000*	Expected as per AAD
<45	13	58.5	0.008	13	13.7	0.002
45-54	54	72.5	0.039	54	49.6	0.027
55-64	118	71.8	0.085	118	32.3	0.038
65-74	158	80.4	0.127	158	22.5	0.036
75+	46	150.2	0.069	46	40.1	0.018
Total	389		0.328	389		0.121

*Number of rasagiline participants from the MRF file by gender and age category

FDA Table 63: Comparison of the Expected rate of Melanoma in the Rasagiline Development Program using the AAD Screening Program as a Reference Population

Melanomas	Number Observed *	Number Expected **	Obs./ Exp. Ratio	95% CI ***
Invasive	4	1.52	2.6	0.72, 6.74
In Situ	6	0.59	10.2	3.7, 22.1
Total	10	2.11	4.7	2.3, 8.7

* Number of melanoma diagnosed in North American study participants after institution of skin examination for melanoma screening.

** Number of melanomas expected within rasagiline subjects as per the rates of the screened population within the AAD screening program

FDA Table 64: Time to Melanoma Diagnosis for Cases Used in the AAD Screening Data Comparison

Patient ID	Melanoma Type	Exposure at Diagnosis	Detected at Which Screening*
1. PRESTO #209	Invasive	6 months	First Examination
2. PRESTO Ext. #424	Invasive	7 months	First Examination
3. PRESTO Ext. #271	Invasive	14 months	Sixth Examination
4. TEMPO Ext. #544	Invasive	47 months	Fourth Examination
5. TEMPO Ext. #064	In situ	41 months	Second Examination
6. PRESTO Ext. #494	In situ	5 months	First Examination
7. PRESTO Ext. #520	In situ	9 months	First Examination
8. PRESTO #169	In situ	6 months	Third Examination
9. PRESTO #613	In situ	6 months	Second Examination
10. TEMPO Ext. #116	In situ	42 months	First Examination

* This column pertains to which of the Information regarding which of the subject's dermatologic screening examinations the melanoma was detected. The information was obtained via e-mail communication with Teva, received 6/9/2004.

As compared to the number of melanomas expected by rates within the American Academy of Dermatology screening program, the observed number of melanomas within the rasagiline development program was not more than expected for invasive melanomas, but was more than expected (Incidence Density Ratio: 10.2, 95% Confidence Interval: 3.7, 22.1) for in situ melanomas.

A second comparison to the AAD data was done in which the observed cases were restricted to those diagnosed during the subjects first dermatologic screening within the development program. This was done to address the fact that the AAD data was generally a one time examination for most subjects (as noted above, about 22% percent of AAD subjects stated they had been screened previously in the AAD program), while subjects in the rasagiline development program were screened every three months, and thus had more time and opportunity for a melanoma to be uncovered.

Of the total 10 melanomas occurring in North American study participants after active screening commenced, five were diagnosed during the subjects' first screening examination and five were diagnosed in examinations *after* the first screening examination. For the five diagnosed after following the first screening examination, two were found on the subjects' second examination, one was found during the subjects third examination, one was found in the subjects fourth examination, and one in the subjects sixth screening (See table above).

FDA Table 65: Comparison of the Expected rate of Melanoma in the Rasagiline Development Program using the AAD Screening Program as a Reference Population: Observed Cases Restricted to those Diagnosed during Initial Screening

Melanomas	Number Observed *	Number Expected **	Obs./ Exp. Ratio	95% CI ***
Invasive	2	1.52	1.3	0.16, 4.75
In Situ	3	0.59	5.1	1.05, 14.9
Total	5	2.11	2.4	0.8, 5.5

* Number of melanoma diagnosed in North American study participants after institution of skin examination for melanoma screening

** Number of melanomas expected within rasagiline subjects as per the rates of the screened population within the AAD screening program

When the comparison of the observed number of melanomas during the rasagiline development program is restricted to the five diagnosed during the subjects' first dermatologic screening, the number of in situ melanomas remained statistically elevated, but the lower boundary of the confidence interval is only minimally higher than equivalence. It should be stressed, however, that the AAD screening population was a particularly high risk group. For example, while an estimated 1% of the United States general population reports a family history of melanoma, while 14% of AAD participants did so.

5.5.4 Data from other Parkinson's Disease Therapy Development Programs

In an effort to establish a more appropriate comparison group for melanoma in the Parkinson's disease clinical trial population, the DNDP requested datasets for clinical development trials from the sponsors of other Parkinson's disease therapies. The datasets included details on the total controlled and extension studies, as well as on the occurrence of melanoma. The requests were sent in November 2001 to the following sponsors: GlaxoSmithKline (ropinirole), Orion (entacapone), Pharmacia & Upjohn (pramipexole), Hoffman-Larouche (tolcapone), Bristol Myers Squibb (levodopa-carbidopa), Lilly (pergolide) and Somerset (selegiline).

Exposure and case information for the five datasets submitted is summarized in the table below (Details of calculations and individuals cases are included in the Attachment 9.26 of this review). The rate of melanoma within the rasagiline development program falls within the range of rates seen in the other development programs. In fact, the tolcapone development program had a higher rate of melanoma than the rasagiline development program. The Division did not receive responses from Somerset or Bristol Myers Squibb regarding rate of melanoma in the selegiline and Sinemet CR development programs.

FDA Table 66: Summary of melanoma occurrence in PD therapy development programs

Sponsor	Principle Medication In Studies*	Total Subjects	Total PYs	Mel. Cases	% (Case/Pts)	Incidence Density per 1000 PYs
Lilly	Pergolide	942	930	0	N/A	N/A
Pharmacia	Pramipexole	5881	6909	11	0.19	1.6
GSK	Ropinirole	3138	3377	1	0.031	0.3
Orion	Entacapone	2202	2486	0	N/A	N/A
Hoffman-LaRouche	Tolcapone	2847	3200	33	1.16	10.3
Teva	<i>Rasagiline</i>	1935**	2450**	20	1.03	8.2

Abbreviations: RCT - Randomized Controlled Trials, Ext – Extension Study, PY – Person Years

* Some of the PD therapy development studies included active control arms other than the drug being investigated

**120-day safety update, Section 2.1.1

Reviewer comment: The table above demonstrates a wide range of melanoma rates. Of note is the substantial difference between members of the same class of medication, including the dopamine agonists (pramipexole, ropinirole), and the COMT inhibitors (entacapone, tolcapone).

Several factors may account for the difference in melanoma rates between the various development programs. One is ascertainment bias, and there may have been differential vigilance in ascertaining skin cancers in the various trials.

A second possibility is that the difference may reflect the geographic location of the various trials, consistent with Teva's observation that rates of melanoma, and skin cancers in general, were considerably higher among participants in the North American studies than elsewhere. The percentage of subjects from North American trials for each of the anti-Parkinsonian therapies is as follows:

FDA Table 67: Percentage of trials conducted in North America for the various PD Therapy Development Programs

Development Program	RCTs in North America/Total	Extension Trials in North	% of Subjects from Trials in	Melanoma Incidence

	<i>[# Trials (Pts.)]</i>	<i>Amer./Total [# Trials (Pts.)]</i>	<i>North America Only</i>	<i>Density per 1000 PYs</i>
<i>Entacapone</i>	<i>1(205)/5(1303)</i>	<i>2(194)/6(899)</i>	<i>18</i>	<i>N/A*</i>
<i>Ropinirole</i>	<i>3(515)/13(2238)</i>	<i>2(123)/9(710)</i>	<i>22</i>	<i>0.3</i>
<i>Pramipexole</i>	<i>8(1534) /19(3771)</i>	<i>4(938)/13(2874)</i>	<i>37</i>	<i>1.6</i>
<i>Tolcapone</i>	<i>4(876)/8(1450)</i>	<i>4(625)/9(1397)</i>	<i>53</i>	<i>10.3</i>
<i>Rasagiline</i>	<i>2(876)/3(1563)</i>	<i>2(644)/3(1124)</i>	<i>56</i>	<i>8.2</i>
<i>Pergolide</i>	<i>**</i>	<i>**</i>	<i>**</i>	<i>**</i>

*No cases of melanoma were reported in the entacapone development trial

** The trial information in the pergolide dataset did not contain sufficient detail to ascertain the percentage of North American and Non-North American subjects.

Based upon the general calculation above, there does appear to be a correlation between a higher percentage of trials conducted in North American and the number of melanoma cases recorded during the trial, with the highest incidence density of cases (10.3 per 1000 PYs) found in the tolcapone development program, which utilized the largest percentage of North American subjects (53%). Likewise, differences in melanoma rates between various members of the same medication class also appeared to reflect the percentage of trials in North America.

Varying rates of non-Caucasian subjects within the development programs was also considered as a possible contributor to the range of melanoma rates. However, the large majority of subjects within all the development programs analyzed were Caucasian: entacapone 98%, tolcapone 97%, pramipexole 96%, and pergolide 98%.¹⁴⁰

5.5.5 Placebo-Controlled Portions of TEMPO, LARGO and PRESTO.

While most of the melanoma cases within the rasagiline development program were identified during phases of the clinical trials without placebo control, five melanomas were diagnosed during the placebo-controlled portions of the three, Phase III studies. These included:

1. TEMPO: Rasagiline arm: 1 melanoma in 121 person-years
Placebo arm: 0 melanomas in 63 person-years
2. PRESTO: Rasagiline arm: 3 melanomas in 146 person-years
Placebo arm: 0 melanomas in 74 person-years
3. LARGO: Rasagiline arm: 0 melanomas in 77 person-years
Placebo arm: 1 melanoma in 74 person-years.

However, by Poisson analysis the difference in cases between the rasagiline (all doses combined) and placebo study arms was not found to be statistically significant for the three trials combined, or in TEMPO or PRESTO individually.¹⁴¹¹⁴²¹⁴³

¹⁴⁰ The percentage of Caucasian subjects in the ropinirole development program was not located in an initial search of the FDA safety review, and so is not included in the listing given here.

¹⁴¹ For TEMPO, PRESTO and LARGO combined: Rasagiline-treated subjects (4 cases/344 person-years), Poisson Exact test – 95% Confidence Interval: 0.003, 0.30, Placebo-treated subjects (1 case/210 person-years): Poisson Exact test – 95% Confidence Interval: 0.0001, 0.23.

5.5.6 Logistic Regression

A logistic regression analysis was considered, in which the contribution of various variables within the rasagiline development program dataset (age, levodopa treatment, duration of rasagiline treatment, geographic location, and other melanoma risk factors) could be assessed for their association with melanoma. However, the number of cases of melanoma was too low to support such modeling.

5.6 Conclusions

The analyses and other considerations of the occurrence of melanoma in the rasagiline development program yielded mixed results. While most aspects were not supportive of a causal relationship between rasagiline treatment and the development of melanomas, other analyses did suggest an increased risk with rasagiline exposure. The specific aspects which were not supportive of a causal association between rasagiline and melanoma included the following:

1. The rate of melanomas observed in the rasagiline development program was within the range of rates seen in five other Parkinson's disease therapy programs, and was exceeded by the rate of one of the four (tolcapone).
2. Although some cases occurred after more extended rasagiline treatment, the latency between rasagiline treatment and detection of the melanoma was generally too short for biological plausibility (range: 2.5 and 55 months, median 13 months, mean 21 months).
3. The rate of melanoma within the rasagiline development trials, and within the other Parkinson's disease therapy development programs for which datasets were submitted, was strongly associated with the study location of the clinical trials. Specifically, studies conducted within North America had higher rates of melanoma than those conducted outside North America.
4. There has been a history of case reports associating melanoma with Parkinson's disease and in particular with levodopa treatment. Although the literature on the subject is limited to case reports, my assessment is that the examination of this issue in the literature has suggested that confounding factors, rather than medication, were responsible for the association.
5. Melanoma rates are rising rapidly worldwide, making the upper limit of the expected number of cases difficult to ascertain. In addition, the rate of melanoma identification in the rasagiline development program increased considerably following the commencement of dermatologic screening for melanoma, which also complicates the determination of the number of expected cases.

Elements of data that are suggestive of an elevated risk include the following:

¹⁴² For TEMPO: Rasagiline-treated subjects: Poisson Exact test - 95% Confidence Interval: 0.0002, 0.05. Placebo-treated subjects: Poisson Exact test - 95% Confidence Interval: 0, 0.06.

¹⁴³ For PRESTO : Rasagiline-treated subjects - 95% Confidence Interval: 0.004, 0.06.; Placebo-treated subjects: Poisson Exact test - 95% Confidence Interval: 0, 0.05

1. The number of melanomas within the rasagiline development program was more than would be expected based upon the rate of melanoma in the general population, as reported to SEER. This is true even when the analysis is restricted to invasive melanomas (for which the reporting to SEER is considered more accurate) and possible under-reporting to the SEER database is corrected by a factor of two- and three-fold.
2. As compared to the number of melanomas expected by rates within the American Academy of Dermatology screening program, the observed number of melanomas within the rasagiline development program was not more than expected for invasive melanomas, but was more than expected (Incidence Density Ratio: 10.2, 95% Confidence Interval: 3.7, 22.1) for in situ melanomas.

5.6.1 Phase IV Randomized Controlled Trial

While the data accumulated during the rasagiline development program is generally not supportive of a causal association between rasagiline and melanoma, the analysis is limited by the lack of a demographically equivalent, parallel control group. It is therefore recommended that Teva fully address this question through a Phase IV agreement by conducting a randomized controlled trial in rasagiline-exposed and unexposed Parkinson's disease patients to measure melanoma incidence.

A randomized controlled trial is suggested as this design has the greatest likelihood of producing treatment and control groups that are equivalent except for the exposure of interest. Parkinson's disease patients (both newly diagnosed and those already on levodopa therapy) could be recruited through their outpatient providers. To control for geographic variation in background rates, it is recommended that subjects either be drawn from a single general location, or preferably that equivalent numbers of rasagiline exposed and unexposed subjects be drawn from various geographic areas. Given the much lower risk of melanoma among persons with increased melanin content in their skin, subject recruitment could be restricted to Caucasian subjects only.

Baseline information for cohort members would include demographic information, information on melanoma risk factors and past diagnosis of skin cancer, as well as information on current and past Parkinson's disease therapies. Subjects would then be monitored through questionnaires (yearly or twice a year) inquiring about interim changes in Parkinson's disease therapies. Active screening for melanoma (once every three months) is recommended, as this will enhance the likelihood of complete melanoma detection and minimize the potential confounder of differing access to medical care. Upon study entry, subjects should also be given basic information on skin cancers and self-examination for suspicious lesions upon study entry.

6. Review of Systems

In the following sections, I review safety data by body system. Teva's presentation divided adverse events by body system, and for consistency I generally utilized Teva's groupings and terminology. However, Teva included psychiatric AEs within the nervous

system, while I divided psychiatric and nervous system AEs into two separate categories. Teva also included cerebrovascular accidents within the cardiovascular system, whereas I discuss cerebrovascular accidents as part of the nervous system. The sponsor tables and other sources from which the information in the ROS was obtained are listed in Attachments 9.29 of this review.

In the ROS, I generally note the number of adverse events occurring in 1% or more of rasagiline-treated subjects. Adverse events that occurred in 1% or more of rasagiline-treated subjects and which were more than twice as frequently reported as in the placebo group are emphasized via underlining.

6.1 Cardiovascular (CV)

(Includes general CV Disorders, Heart Rate and Rhythm Disorders, and Myo-, Endo- and Pericardial disorders)

Deaths: No deaths in rasagiline-treated subjects were specifically classified as CV in nature. However, two subjects whose death was classified as “Sudden Death” may have experienced cardiac arrest. These deaths included a 68 year-old man with severe CAD on autopsy who died suddenly while snorkeling on vacation, and a 77 year-old man with Alzheimer’s disease and a history of heavy smoking who died in his sleep. A third participant classified by the sponsor as cause of death “Unknown” was found dead in an overheated apartment. Her death was speculated to have been due to cardiac arrest precipitated by heat exposure.

SAEs: No single CV SAE occurred in more than 1% of rasagiline-treated subjects in the two placebo-controlled cohorts. For Cohort 1 (monotherapy), 1.7% of rasagiline-treated subjects and no placebo-treated subjects reported CV SAEs. The only CV SAE affecting more than one rasagiline-treated subject were angina pectoris (rasagiline 1.0%, n=3; placebo n=0). One subject each reported an SAE of atrial fibrillation, cardiac arrest, and myocardial infarction, compared to none in the placebo group.

In Cohort 2 (levodopa adjunct), CV SAEs were reported by 2.9% of rasagiline 1 mg subjects and 2.3% of placebo subjects. CV SAEs experienced by two or more rasagiline-treated subjects were arrhythmia (rasagiline 0.5%, n=2; placebo n=0), postural hypotension (rasagiline 0.5%, n=2; placebo n=0) and heart failure (rasagiline 0.5%, n=2; placebo 0.8%, n=3).

Syncope (1.1%, n=15) and angina pectoris (1.2%, n=14) were the only CV SAEs in Cohort 9 (all PD patients exposed to rasagiline) reported by at least 1% of subjects. Notable CV SAEs reported by two or more subjects in Cohort 9 included heart failure (0.4%, n=5), hypertension (0.5%, n=7), myocardial infarction (0.4%, n=6), arrhythmia (0.3%, n=4), arteriosclerosis (0.1%, n=2), atrial fibrillation (0.6%, n=8), coronary artery disorder (0.5%, n=7) and hypotension (0.4%, n=6).

Discontinuations: In Cohort 1, the only CV AE leading to discontinuation in rasagiline subjects (1 mg/day) was hypertension (0.7%, n=1), compared to none in placebo. For

Cohort 2, 1.3% of participants in the rasagiline group (n=5), and 0.8% in the placebo group (n=3) discontinued due to CV AEs. One participant each in the rasagiline 1 mg group of Cohort 2 discontinued due to arrhythmia, AV block complete or heart failure, compared to one or none¹⁴⁴ for placebo.

In Cohort 9, no CV AE led to discontinuation in more than 1% of subjects. CV AEs leading to discontinuation in more than one subject were hypertension (0.7%, n=9), postural hypotension (0.5%, n=7), syncope (0.4%, n=5), blood pressure fluctuation (0.1%, n=2), atrial fibrillation (0.1%, n=2) and tachycardia (0.1%, n=1).

AEs: In Cohort 1, CV AEs occurring in more than 1% of rasagiline-treated subjects were postural hypotension (rasagiline 3.1%, n=9; placebo 4.6%, n=7), hypertension (rasagiline 2.0%, n=6; placebo 4.0%, n=6), angina pectoris (rasagiline 1%, n=3; placebo n=0), and palpitation (rasagiline 1%, n=3; placebo 2%, n=3).

For Cohort 2, the only CV AEs reported in more than 1% of rasagiline-treated subjects (1 mg/day) were postural hypotension (rasagiline 4.7%, n=18; placebo 1.3%, n=5), hypotension (rasagiline 2.1%, n=8; placebo 1.8%, n=7), hypertension (rasagiline 1.3%, n=5; placebo 2.6%, n=10), and first degree AV block (rasagiline 1.1%, n=4; placebo 0.5%, n=2).

In Cohort 9, the only CV AEs reported in more than 1% of participants were postural hypotension (7.8%, n=106), syncope (2.4%, n=33), hypotension (1.8%, n=24), angina pectoris (1.5%, n=21), vasodilatation (1.3%, n=18), and palpitation (1.0%, n=14).

Other Safety Issues: Although the sponsor's ECG evaluation did not reveal important differences in QT prolongation or other ECG abnormalities between the rasagiline and placebo treatment groups in the adjunctive studies, the ECG data collected was inadequate, with significantly limited information for subjects in Cohort 1 and the Phase I/II studies. Vital sign analysis was notable for a higher percentage of rasagiline-treated subjects (13.4%) in the levodopa adjunct cohort experiencing postural hypotension than placebo-treated subjects (8.5%); this is corroborated by the excess of postural hypotension AEs in the rasagiline group compared to the placebo group in Cohort 2.

Outstanding issues:

- Teva's analysis of the ECG data from Cohort 1 and the Phase I/II studies is inadequate. Although the data from Cohort 2 are not suggestive of an effect of rasagiline on cardiac repolarization, there is no way to know whether the concomitant levodopa used in Cohort 2 may have had some protective effect on cardiac repolarization. It is therefore important to know what effect rasagiline in monotherapy has on cardiac repolarization.

In response to my initial query for a more complete analysis of the Cohort 1 data, Teva stated that this was not immediately possible due to the limited nature of the

¹⁴⁴ One placebo subject (0.3%) in the rasagiline levodopa adjunctive cohort (Cohort 2) discontinued due to heart failure, while none discontinued due to arrhythmia, AV block or blood pressure fluctuations.

original ECG data coding from TEMPO. However, as it is presumed that Teva has retained the original ECG tracings, we will request that the original TEMPO tracings be overread in the same manner (through _____ that was utilized in the Cohort 2 (levodopa adjunct) studies.

6.2 Gastrointestinal (GI)

(Includes GI, Hepatic and Biliary System Disorders)

Deaths: During the rasagiline development program, two rasagiline-treated subjects died from GI-related causes: one from colon carcinoma, and another due to volvulus and megacolon complicated by sepsis, pneumonia, and pulmonary embolism. The latter subject's death is also noted in the Vascular section 6.10. One entacapone-treated subject and no placebo-treated subjects died of GI-related causes.

SAEs: In Cohort 1 (monotherapy), no GI SAE occurred in more than 1% of rasagiline-treated subjects. The only SAE experienced by more than one subject was colitis (rasagiline n=2, 0.7%; placebo n=0). Constipation, intestinal obstruction, nausea and vomiting were reported as SAEs for one rasagiline-treated subject each, compared to none for placebo.

For Cohort 2 (levodopa adjunct therapy), SAEs reported by rasagiline-treated subjects were intestinal obstruction (rasagiline 0.5%, n=2; placebo n=0), fecal impaction (rasagiline 0.3%, n=1; placebo n=0) and megacolon (rasagiline 0.3%, n=1; placebo n=0). The subject experiencing megacolon was the same subject reported in the *Deaths* section immediately above, and details of his clinical presentation and subsequent death are provided in Attachments 9.2.

In Cohort 9 (all PD subjects patients exposed to rasagiline), GI SAEs reported by more than one participant were intestinal obstruction (0.4%, n=6), gastrointestinal hemorrhage (0.3%, n=4), dyspepsia (0.2%, n=3), cholecystitis (0.2%, n=3), cholelithiasis (0.2%, n=3), colitis (0.2%, n=3), constipation (0.2%, n=3), gastrointestinal disorder (0.1%, n=2) and gastrointestinal carcinoma (0.3%, n=4). The four cases of gastrointestinal carcinomas were all colon cancers, two of which were identified by polyp biopsy during routine screening.

Discontinuations: In the placebo-controlled cohorts, no GI event led to discontinuation of at least 1% of rasagiline subjects. No rasagiline-treated subjects in Cohort 1 discontinued due to a GI event. For Cohort 2, one participant each (0.3%) in the rasagiline 1mg group discontinued due to constipation (placebo n=0), dyspepsia (placebo n=0), gastrointestinal hemorrhage (placebo n=0), vomiting (placebo n=1, 0.3%) and nausea (placebo n=6, 1.5%). In Cohort 9, the only GI AEs leading to discontinuation in more than one subject were gastrointestinal carcinoma (0.2%, n=3), gastrointestinal hemorrhage (0.1%, n=2), dyspepsia (0.1%, n=2), diarrhea (0.1%, n=2), and constipation (0.1%, n=2).

AEs: For Cohort 1, the only AEs reported by more than 1% of rasagiline-treated subjects were dyspepsia (rasagiline 5.8%, n=17; placebo 4.0%, n=6), nausea (rasagiline 5.4%,

n=16; placebo 7.3%, n=11), diarrhea (rasagiline 5.1%, n=15; placebo 6.0%, n=9), constipation (rasagiline 3.7%, n=11; placebo 4.0%, n=6), dry mouth (rasagiline 2.0%, n=6; placebo 4.0%, n=6), tooth disorder (rasagiline 1.7%, n=5; placebo 0.7%, n=1) flatulence (rasagiline 1.4%, n=4; placebo n=0), and liver function tests abnormal (rasagiline 1.4%, n=4; placebo 1.3%, n=2).

In Cohort 2, AEs reported by 1% or more of rasagiline-treated subjects (1 mg/day) were nausea (6.8% rasagiline, n=26; 5.9% placebo, n=23), constipation (4.2% rasagiline, n=16; 2.1% placebo, n=8), vomiting (3.4% rasagiline, n=13; 1.0% placebo, n=5), dry mouth (3.4% rasagiline, n=13, 1.8 % placebo, n=7), dyspepsia (2.9% rasagiline, n=11; 2.3% placebo, n=9), and anorexia (2.1% rasagiline, n=8; 0.5% placebo, n=2).

In Cohort 9, GI AEs reported by more than 1% of subjects were nausea (11.5%, n=168), constipation (6.7%, n=111), dyspepsia (5.5%, n=81), diarrhea (5.3%, n=82), liver function tests abnormal (4.2%, n=41), vomiting (3.6%, n=52), dry mouth (2.6%, n=47), anorexia (1.4%, n=23), flatulence (2.3%, n=22), tooth disorder (1.9%, n=31), gastrointestinal disorder (1.1%, n=22) and dysphagia (5.5%, n=81)

Other Safety Issues: Analyses of laboratory data did not suggest rasagiline-related changes in AST, ALT, or total bilirubin. There were no cases of acute hepatic failure or pancreatitis in rasagiline-treated subjects. I searched the ISS, 120-Day Safety Update, Phase III study reports and the Cohort 9 AE dataset for cases of constipation, and found no evidence that any cases of constipation had resulted in megacolon or required surgical intervention.¹⁴⁵

6.3 Central and Peripheral Nervous System (CPNS)

Deaths: In the Cohort 2 placebo-controlled study PRESTO, two deaths from cerebrovascular accidents occurred in rasagiline-treated subjects (0.6%), compared to none in the placebo group. An additional four rasagiline subjects in extension trials without placebo controls died of cerebrovascular accidents, for a total of six rasagiline-treated subjects. No other rasagiline subjects died due to a CPNS cause.

SAEs: No CPNS SAEs occurred in more than 1% of rasagiline subjects in the placebo-controlled cohorts. The most frequent CPNS SAEs in the rasagiline monotherapy cohort (Cohort 1) were confusion, depression, dizziness, dysarthria, somnolence and tremor, each occurring in one rasagiline-treated participant (0.3%). For placebo, dizziness and tremor occurred in one subject each (0.7%), while confusion, depression, dysarthria and somnolence were reported in none.

For Cohort 2 (levodopa adjunct), one (0.3%) rasagiline-treated subject (1 mg/day) experienced each of the following SAEs: dizziness (placebo n=1, 0.3%), dystonia (placebo n=0), extrapyramidal syndrome (placebo 0.5%, n=2), meningitis (placebo n=0), and spinal stenosis (placebo n=0). Two (0.5%) rasagiline 1 mg subjects experienced a

¹⁴⁵ LARGO # 16006 experienced megacolon, but as per the sponsor narrative this was precipitated by intestinal volvulus.

cerebrovascular accident, compared to one (0.3%) placebo subject. In Cohort 9 (all PD patients exposed to rasagiline), no SAE was reported by at least 1% of subjects. The most frequent CPNS SAEs were cerebrovascular accident (0.7%, n=10), spinal stenosis (0.7%, n=9), extrapyramidal syndrome (0.5%, n=7), confusion (0.4%, n=6), dizziness (0.4%, n=5), and neuropathy (0.3%, n=4).

Discontinuations: For Cohort 1, the only CPNS AEs leading to discontinuation in rasagiline 1 mg subjects were dizziness (rasagiline 0.7%, n=1; placebo n=0) and cerebrovascular disorder (rasagiline 0.7%, n=1; placebo n=0). In Cohort 2, no AE led to discontinuation in more than 1% of rasagiline 1 mg participants, and the only AE leading to discontinuation in more than one subject was dizziness (rasagiline 0.5%, n=2; placebo 0.8%, n=3). One subject each in the placebo and rasagiline groups of Cohort 2 discontinued due to a cerebrovascular accident. In Cohort 9, no CPNS AE led to the discontinuation of more than 1% of subjects. The most frequently reported AEs resulting in discontinuation were dizziness (0.6%, n=8), dyskinesia (0.4%, n=5), extrapyramidal syndrome (0.3%, n=4), paresthesia (0.3%, n=3) and cerebrovascular accident (0.2%, n=3).

AEs: In Cohort 1, AEs occurring in at least 1% of rasagiline-treated subjects were dizziness (rasagiline 11.4%, n=17; placebo 10.6%, n=16), paresthesia (rasagiline 2.0%, n=3; placebo 1.3%, n=2), and vertigo (rasagiline 2.0%, n=3; placebo 0.7%, n=1).

For Cohort 2, AEs reported by at least 1% of rasagiline (1 mg)-treated subjects were dyskinesia (rasagiline 10.4%, n=40; placebo 6.4%, n=25), dizziness (rasagiline 5.3%, n=20; placebo 4.9%, n=19), and dystonia (2.4% rasagiline, n= 9; 0.8% placebo, n=3).

In Cohort 9, AEs occurring in 1% or more of cohort members were: dizziness (12.8%, n=174), dyskinesia (10.7%, n=145), extrapyramidal syndrome (5.4%, n=73), hypertonia (4.6%, n=63), ataxia (2.6%, n=35), amnesia (1.9%, n=26), abnormal gait (1.3%, n=17), dystonia (1.9%, n=26), spinal stenosis (1.0%, n=14) and cerebrovascular accident (1.0%, n=13)

6.4 Psychiatric

Deaths: No participant in the rasagiline development program died and had a psychiatric condition listed as the cause of death.

SAEs: In neither of the two placebo-controlled cohorts were psychiatric SAEs experienced by more than 1% of rasagiline-treated subjects. For Cohort 1 (monotherapy), one rasagiline-treated subject each experienced the SAEs of confusion, depression, and somnolence, compared to none in the placebo group. In Cohort 2 (levodopa adjunct), no psychiatric SAEs were reported. In Cohort 9 (all PD patients exposed to rasagiline), SAEs reported by more than one subject were depression (0.4%, n=6), hallucinations (0.4%, n=5), psychosis (0.4%, n=5) and anxiety (0.2%, n=3).

Discontinuations: In Cohort 1, three rasagiline-treated (1 mg/day) subjects discontinued due to hallucination, compared to none in the placebo group. For Cohort 2, two rasagiline subjects discontinued due to hallucinations, compare to one in placebo. One rasagiline subject in Cohort 2 discontinued due to personality disorder (placebo n=0), and another due to somnolence (placebo n=1).

In Cohort 9, AEs leading to discontinuation in more than one subject were hallucinations (1.0%, n=14), depression (0.4%, n=6), psychosis (0.3%, n=4), sleep disorder (0.2%, n=3), thinking abnormal (0.1%, n=2), agitation (0.1%, n=2) and anxiety (0.1%, n=2).

AEs: For Cohort 1, AEs occurring in more than 1% of rasagiline subjects were depression (rasagiline 5.4%, n=8; placebo 2.0%, n=3), sleep disorder (rasagiline 5.1%, n=15; placebo 4.0%, n=6), abnormal dreams (rasagiline 2.0%, n=6; placebo n=0), anxiety (rasagiline 2.0%, n= 6; placebo 3.3%, n=5), somnolence (rasagiline 2.0%, n=6; placebo 1.3%, n=2), and hallucinations (rasagiline 1.4%, n=4; placebo 0.7%, n=1).

For Cohort 2, AEs reported by more than 1% of rasagiline subjects were sleep disorder (rasagiline 5.0%, n=19; placebo 4.1%, n=16), somnolence (rasagiline 3.2%, n=12; placebo 2.3%, n=9), hallucinations (rasagiline 2.9%, n=11; placebo 2.1%, n=8) and abnormal dreams (rasagiline 2.1%, n=8; placebo 0.8%, n=3).

In Cohort 9, AEs experienced by more than 1% of subjects were sleep disorder (11.8%, n=161), somnolence (8.1%, n=110), hallucinations (5.2%, n=72), anxiety (4.5%, n=61), abnormal dreams (3.3%, n=45), confusion (2.4%, n=33), and nervousness (1.1%, n=15).

6.5 Respiratory

Deaths: Pneumonia was considered a significant causal factor in the deaths of four rasagiline-treated participants, and in two of the four it was considered the primary cause. In addition, two of these four subjects also experienced a pulmonary embolism as a contributor in their deaths (these subjects are also included in the Vascular section 6.10). Two entacapone-treated subjects died of pneumonia, while no placebo subjects did. One entacapone-treated subject died due to a pulmonary embolism.

SAEs: In Cohort 1 (placebo-controlled monotherapy), no rasagiline-treated subject reported a respiratory SAE. For Cohort 2 (levodopa adjunct), one rasagiline (1 mg) subject each (0.3%) experienced SAEs of bronchitis (placebo n=0), dyspnea (placebo 0.3%, n=1) and respiratory disorder (placebo n=0). In Cohort 9 (all PD patients exposed to rasagiline), the following respiratory SAEs were reported in more than one participant: dyspnea (0.3%, n=4), bronchitis (0.3%, n=3), and pneumonia (0.3%, n=3). The following SAEs occurred in one participant (0.1%) each: aspiration pneumonia, asthma, emphysema, epistaxis, lung disorder and pharyngeal carcinoma.

Discontinuations: No rasagiline-treated participants in Cohort 1 discontinued due to a respiratory AE. For Cohort 2, the only respiratory AE leading to discontinuation was dyspnea (rasagiline 0.5%, n=2; placebo 0.3%, n=1). In Cohort 9, dyspnea (0.2%, n=3)

and pneumonia (0.1%, n=2) were the only AEs leading to discontinuation in more than one subject.

AEs: For Cohort 1, AEs reported in 1% or more of rasagiline-treated subjects were cough increased (rasagiline 4.1%, n=12; placebo 5.3%, n=8), sinusitis (rasagiline 3.1%, n=9; placebo 4.0%, n=6) pharyngitis (rasagiline 2.4%, n=7; placebo 2.6%, n=4), rhinitis (rasagiline 2.0%, n=6; placebo 1.3%, n=2), respiratory disorder (rasagiline 1.0%, n=3; placebo 4.0%, n=6) and bronchitis (rasagiline 1.0%, n=3; placebo 0.7%, n=1).

In Cohort 2, 1% or more of rasagiline (1 mg)-treated subjects experienced the following AEs: dyspnea (rasagiline 2.1%, n=8; placebo 1.3%, n=5), cough increased (rasagiline 1.3%, n=5; placebo 1.3%, n=5), pharyngitis (rasagiline 1.1%, n=4; placebo 1.3%, n=5) and sinusitis (rasagiline 1.1%, n=4; placebo 1.3%, n=5).

For Cohort 9, AEs occurring in 1% or more of cohort members were sinusitis (4.4%, n=60), cough increased (4.2%, n=57), pharyngitis (3.1%, n=42), dyspnea (2.9%, n=39), bronchitis (2.4%, n=33), rhinitis (2.4%, n=32) and epistaxis (1.3%, n=17).

6.6 Musculoskeletal (MS)

Deaths: No participant in the rasagiline development program had a musculoskeletal condition listed as their cause of death.

SAEs: No rasagiline-treated subjects in Cohort 1 (monotherapy) experienced a MS SAE. For Cohort 2 (levodopa adjunct) the only MS SAE occurring in a rasagiline-treated participant was arthritis (rasagiline 0.3%, n=1; placebo 0.3%, n=1). For Cohort 9 (all PD subjects exposed to rasagiline), no SAE occurred in more than 1% of subjects. The only SAEs reported for more than one subject in Cohort 9 were joint disorder (0.7%, n=7) arthralgia (0.3%, n=3), arthritis (0.3%, n=3) and rhabdomyolysis (0.2%, n=2).

Rhabdomyolysis was reported in two subjects receiving rasagiline (0.5 mg) as a levodopa adjunct. Both cases followed a fall and prolonged immobilization. The first subject, who had a history of chronic renal insufficiency, was reported in the initial NDA to have become lethargic, experienced hallucinations, and lost consciousness. Teva later forwarded notes from the site investigator, who suggested that the subject may have become entangled in a blanket and been unable to extricate himself, but did not experience significant changes in mental status. His CPK value was not submitted by the sponsor at the time of the initial NDA. The subject's CPK value was within normal limits (78 IU/L, with normal range of 61 to 224 IU/L) two days following the fall.¹⁴⁶ (There were presumably no earlier values.) Teva stated it was unclear how the investigator had reached the diagnosis of rhabdomyolysis.

The second subject took an excess of trihexphenidyl, developed a suspected drug-induced delirium, fell and was unable to rise for some time. His CPK was 9735 U/L on hospital

¹⁴⁶ E-mail responses from Teva received on March 31, 2004 and April 12, 2004

admission. Teva stated that both discontinued the study although they recovered to their baseline.

Discontinuations: No rasagiline-treated participant in either of the placebo-controlled cohorts (Cohort 1 or 2) discontinued due to a MS AE. In Cohort 9, the only MS AE leading to discontinuation was arthralgia (n=1, 0.1%).

AEs: For Cohort 1, AEs occurring in more than 1% of rasagiline-treated subjects were arthralgia (rasagiline 7.4%, n=11; placebo 4.0%, n=6), arthritis (rasagiline 2.0 %, n=3; placebo 0.7 %, n=1), leg cramps (rasagiline 1.7%, n=4, placebo 1.3%, n=2) myalgia (rasagiline 1.4%, n=4; placebo 2.0%, n=3) and joint disorder (rasagiline 1.4%, n=4, placebo 0.7%, n=1). For Cohort 2, the only treatment emergent AEs occurring in more than 1% of rasagiline-treated (1 mg/day) subjects were arthralgia (rasagiline 3.2%, n=12; placebo 1.3%, n=5) and tenosynovitis (rasagiline 1.3%, n=5; placebo n=0).

MS AEs occurring in 1% or more of Cohort 9 members were arthralgia (10.7%, n=146), joint disorder (3.3%, n=35), leg cramps (3.3%, n=45), arthritis (3.1%, n=42), joint disorder (3.3%, n=45), myalgia (1.8%, n=25), myasthenia (1.8%, n=24), tendon disorder (1.2%, n=16) and bursitis (1.1 %, n=15).

Outstanding Issues: As the two cases of rhabdomyolysis occurred were both confounded by a fall and prolonged immobilization, and one case did not have laboratory confirmation of the diagnosis, we will consider asking the Office of Drug Safety to follow closely for rhabdomyolysis associated with rasagiline treatment in the postmarketing period while holding off on putting rhabdomyolysis in the labeling.

6.7 Metabolic and Nutritional (MN)

Deaths: One rasagiline-treated subject died of a metabolic derangement, although this was an accidental death from carbon monoxide exposure.

SAEs: No rasagiline-treated participants in Cohort 1 (monotherapy) experienced a MN SAE. For Cohort 2 (levodopa adjunct), the only MN SAE was peripheral edema (rasagiline 0.3%, n=1; placebo 0.3%, n=1). For Cohort 9 (all PD patients exposed to rasagiline), dehydration was the only SAE to occur in more than one subject (0.5%, n=6). Alkalosis, hypokalemia, hyponatremia, peripheral edema and weight loss were reported by one subject each.

Discontinuations: No rasagiline-treated participants in Cohort 1 (monotherapy) discontinued due to a MN AE. For Cohort 2 (levodopa adjunct), the only MN AE leading to discontinuation was peripheral edema (rasagiline 0.3%, n=1; placebo 0.3%, n=1). In Cohort 9 (all PD patients exposed to rasagiline), the only MN AE leading to discontinuation of more than one subject was weight loss (0.1%, n=2).

AEs: For Cohort 1, MN AEs reported in rasagiline-treated subjects, and which were more frequent than in placebo subjects, were BUN increased (rasagiline 0.3%, n=1; placebo

n=0) and hyperlipidemia (rasagiline 0.3%, n=1; placebo n=0). In Cohort 2, MN AEs experienced in rasagiline-treated subjects, and which were more frequent than in the placebo group, were weight loss (rasagiline 4.2%, n=16; placebo 1.5%, n=6), weight gain (rasagiline 0.8%, n=3; placebo 0.3%, n=1), gout (rasagiline 0.5%, n=2; placebo n=0), and BUN increased (rasagiline 0.3%, n=1; placebo n=0), hyperlipidemia (rasagiline 0.3%, n=1; placebo n=0), hyperphosphatemia (rasagiline 0.3%, n=1; placebo n=0), hypokalemia (rasagiline 0.3%, n=1; placebo n=0), and lactic dehydrogenase increased (rasagiline 0.3%, n=1; placebo n=0).

AEs occurring in 1% or more of Cohort 9 members were: peripheral edema (8.4%, n=114), weight loss (4.4%, n=60), hyperglycemia (1.8%, n=25), weight gain (1.5%, n=21) and hypercholesterolemia (1.1%, n=15).

Laboratory Data: In Cohort 1 there was an increased percentage of subjects in the rasagiline 1 mg group compared to placebo who experienced a baseline to LOV shift from low/normal to high creatinine (4.1% [rasagiline] versus 2% [placebo]) and blood urea nitrogen (BUN) (4.1% [rasagiline] versus 0.7% [placebo]); however, there was no difference between the treatment groups when the PCS thresholds were utilized. Additionally, no excess of a shift from low/normal to high creatinine and BUN were observed in the rasagiline 1 mg group in Cohort 2. Finally, there was no substantial excess of AEs consistent with renal dysfunction observed in rasagiline treated patients compared to placebo patients (see section 6.8 Urological Reproductive).

6.8 Urological Reproductive (UR)

(Includes Urinary System, Reproductive Male, Female)

Deaths: Two rasagiline-treated subjects died secondary to urologic conditions. One subject died due to carcinoma of the prostate. The second subject died during a hospitalization for a urinary tract infection complicated by pneumonia and cardiopulmonary arrest.

SAEs: In Cohort 1 (monotherapy), the only urologic SAE experienced by a rasagiline-treated subject was prostatic carcinoma (rasagiline 2 mg 0.7%, n=1; placebo n=0). For Cohort 2 (levodopa adjunct), the following SAEs occurred in one rasagiline-treated subject each, compared to none in the placebo group: anuria, bladder carcinoma, pyelonephritis, and urinary retention. In Cohort 9 (all PD patients exposed to rasagiline), the most common SAE was prostate carcinoma, with eleven events reported among nine subjects (0.7%). The only other UR SAE affecting more than one participant was prostate disorder (0.2%, n=3).

Discontinuations: In Cohort 1, the only UR AE leading to discontinuation in rasagiline-treated subjects (1 mg/day) was urinary tract infection (rasagiline 1 mg 0.7%, n=1; placebo n=0). For Cohort 2, the following UR AEs lead to discontinuation of one rasagiline-treated subject each (0.3%): anuria (placebo n=0), dysuria (placebo n=0), and urinary tract infection (placebo 0.3%, n=1). In Cohort 9, the only AE leading to discontinuation in more than one subject was urinary tract infection (0.1%, n=2).

AEs: In Cohort 1, UR AEs occurring in more than one subject receiving rasagiline, and which were more frequent than in placebo, were urinary frequency (rasagiline 1.0%, n=3; placebo n=1, 0.7%), impotence (rasagiline 1.0%, n=3; placebo 0.7%, n=1), albinuria (rasagiline 0.7%, n=2; placebo 0.7%, n=1), prostate specific enzyme increased (rasagiline 0.7%, n=2; placebo n=0), urinary incontinence (rasagiline 0.7%, n=2; placebo 0.7%, n=1), urinary tract infection (rasagiline 0.7%, n=2; placebo 2.6%, n=4) and urinary urgency (rasagiline 0.7%, n=2 placebo n=0).

For Cohort 2, AEs reported for one or more rasagiline (1 mg/day) subjects, and which were more frequent than in placebo, were urinary urgency (rasagiline 0.5%, n=2; placebo 0.3%, n=1), anuria (rasagiline 0.3%, n=1; placebo n=0), dysuria (rasagiline 0.8%, n=3, placebo 0.3%, n=1), kidney pain (rasagiline 0.3%, n=1; placebo n=0), nocturia (rasagiline 0.3%, n=1; placebo n=0), vaginal hemorrhage (rasagiline 0.3%, n=1; placebo n=0), and urogenital anomaly (rasagiline 0.3%, n=1; placebo n=0). The urogenital anomaly occurred in a subject experiencing hematuria, who was found to have a renal cortical cyst and renal pelvis ectasia.

AEs occurring in 1% or more of Cohort 9 members were: urinary tract infection (6.5%, n=88), hematuria (3.9%, n=53), urinary frequency (1.8%, n=24) urinary incontinence (1.5%, n=21), and prostate disorder (1.5%, n=20).

Other safety issues:

- One rasagiline-treated subject (LARGO 16429) experienced acute renal failure following aggressive diuresis during a hospitalization for pacemaker implantation. The subject was reported to recover to baseline with hydration.
- The most frequently detected abnormality on urinalysis was hematuria.
- Eleven cases of prostate cancer in the rasagiline development program were reported by nine rasagiline-treated subjects (0.7%). In a general comparison to other Parkinson's disease development programs, the risk in the rasagiline development program was somewhat higher than the dopamine agonists and entacapone, but lower than tolcapone, although this was based on a small number of subjects. This higher risk may be explained by the increased prevalence of prostate cancer over time related to improved detection (increased use of PSA).

6.9 Skin and Appendages

Deaths: One rasagiline-treated subject died as a result of metastatic melanoma.

SAEs: For Cohort 1 (monotherapy), skin and appendage SAEs for rasagiline-treated subjects were reported for skin melanoma (rasagiline 0.3%, n=1; placebo n=0), skin carcinoma (rasagiline 0.3%, n=1; placebo n=0) and sweating (rasagiline 0.3%, n=1; placebo n=1). In Cohort 2 (levodopa adjunct), skin carcinoma (rasagiline 0.3%, n=1; placebo 0.5%, n=2) and skin melanoma (rasagiline 0.5%, n=2; placebo 0.3%, n=1) were the only SAEs experienced by rasagiline (1 mg) subjects.

For Cohort 9 (all PD patients exposed to rasagiline), the following skin-related SAEs were reported: skin melanoma (1%, n=15), skin carcinoma (0.4%, n=6), sweating (0.1%, n=1) and herpes zoster (0.1%, n=1). There were no AEs suggestive of toxic epidermal necrolysis, Stevens Johnson syndrome, or erythema multiforme.

Discontinuations: No skin-related AEs led to the discontinuation of more than one subject in the two placebo-controlled cohorts. In Cohort 9, the only skin and appendage AEs leading to discontinuation in more than one subject were skin melanoma (0.4%, n=6), rash (0.3%, n=4) and pruritus (0.1%, n=2).

AEs: In Cohort 1, the only AEs reported in at least 1% of rasagiline-treated subjects were rash (rasagiline 3.1%, n=9; placebo 3.3%, n=5), alopecia (rasagiline 1.7%, n=5; placebo 0.7%, n=1), skin carcinoma (rasagiline 1.4%, n=4; placebo 0.7%, n=1) and contact dermatitis (rasagiline 1.0%, n=3; placebo n=0). For Cohort 2, at least 1% or more of rasagiline-treated subjects experienced the following AEs: rash (rasagiline 2.6%, n=10; placebo 1.5%, n=6), sweating (rasagiline 1.6%, n=6; placebo 0.8%, n=3), benign skin neoplasm (rasagiline 1.6%, n=6; placebo 1.3%, n=5), skin carcinoma (rasagiline 1.3%, n=5; placebo 1.5%, n=6) and skin disorder (rasagiline 1.3%, n=5; placebo 1.5%, n=6).

AEs occurring in 1% or more of all Parkinson's disease patients exposed to rasagiline (Cohort 9) were rash (6.0%), benign skin neoplasm (4.1%), sweating (2.5%), pruritus (1.1%), alopecia (1.0%) and skin melanoma (1.0%).

Outstanding Issues:

- The occurrence of 15 cases of melanoma in rasagiline-treated subjects during the development program was investigated by analysis with various reference populations. This is discussed in Section 5.0 of this review. These analyses yielded mixed results, with some elements of the data suggestive of an elevated risk of melanoma associated with rasagiline use, and other elements not supportive of an association. These mixed results, in combination with the large number of confounding factors (such as age and geographic location) and that most cases were identified in study phases without placebo control, preclude reaching a conclusion on the subject from the data accumulated during the development program. For these reasons the FDA will request that Teva conduct a prospective cohort study to address the issue as part of a Phase IV request.

6.10 Vascular

Deaths: One rasagiline-treated subject died due to rupture of an aortic aneurysm, while an entacapone-treated subject died of an aortic dissection. In addition, pulmonary embolus was a contributing factor in the deaths of one rasagiline and one placebo subject.

SAEs: No vascular SAEs affected 1% or more of the rasagiline-treated subjects in the placebo-controlled cohorts. In Cohort 1 (monotherapy), thrombosis and vascular disorder were reported for one rasagiline subject each, compared to none within the placebo group. For Cohort 2 (levodopa adjunct), the only SAEs experienced by rasagiline

subjects were pulmonary embolus (rasagiline 0.5%, n=2; placebo n=0) and thrombosis (rasagiline 0.3%, n=1; placebo n=0).

Cohort 9 members (all PD patients exposed to rasagiline) experienced the following vascular serious adverse events: pulmonary embolus (0.3%, n=4), thrombosis (0.2%, n=2) and vascular disorder (0.3%, n=4).

Discontinuations: In the two placebo-controlled cohorts (Cohort 1 and 2), no early discontinuations due to vascular AEs were reported in rasagiline-treated subjects. For Cohort 9, the vascular SAEs leading to discontinuation were peripheral vascular disorder (1.0%, n=14), vascular disorder (0.5%, n=7), pulmonary embolus (0.3%, n=4), varicose vein (0.4%, n=5), vascular anomaly (0.3%, n=4), deep thrombophlebitis (0.2%, n=3), phlebitis (0.2%, n=3), thrombosis (0.1%, n=2), skin vasculitis (0.1%, n=1) and vasculitis (0.1%, n=1).

AEs: In Cohort 1, vascular adverse events reported by rasagiline-treated subjects included peripheral vascular disorder (rasagiline 0.7%, n=2; placebo n=0), vasodilatation (rasagiline 0.7%, n=2; placebo 2.0%, n=3), thrombosis (rasagiline 0.3%, n=1; placebo n=0), varicose vein (rasagiline 0.3%, n=1; placebo 0.7%, n=1) and vascular disorder (rasagiline 0.7%, n=2; placebo n=0). For Cohort 2, the vascular AEs reported by rasagiline-treated subjects were pulmonary embolus (rasagiline 0.5%, n=2; placebo n=0), thrombosis (rasagiline 0.3%, n=1; placebo n=0) and vascular disorder (rasagiline 0.3%, n=1; placebo 0.5%, n=2).

Cohort 9 members experienced the following vascular adverse events: peripheral vascular disorder (1.0%, n=14), vascular disorder (0.5%, n=7), varicose vein (0.4%, n=5), pulmonary embolus (0.3%, n=4), vascular anomaly (0.3%, n=4), deep thrombophlebitis (0.2%, n=3), phlebitis (0.2%, n=3), thrombosis (0.1%, n=2), vasculitis (0.1%, n=1) and skin vasculitis (0.1%, n=1).

6.11 Hematological and Lymphatic System

(Includes platelet, bleeding, and clotting disorders; Red Blood Cell (RBC), White Blood Cell (WBC) and Reticulo-Endothelial System (RES) disorders; Lymphatic Disorders)

Deaths: One rasagiline-treated subject died of metastatic gastric lymphoma. No subject in the rasagiline development program died of a hematological condition.

SAEs: No rasagiline-treated subjects in either of the two placebo-controlled cohorts (Cohort 1 [monotherapy] and Cohort 2 [levodopa adjunct]) reported a hematologic or lymphatic SAE. For Cohort 9 (all PD patients exposed to rasagiline), anemia (0.2%, n=2) was the only SAE reported in more than one subject, while Hodgkin's lymphoma, myelodysplastic disorder and myeloma were reported for one subject each.

Discontinuations: No rasagiline-treated participants in Cohort 1 discontinued due to a hematologic or lymphatic AE. In Cohort 2, the only hematologic or lymphatic AEs leading to discontinuation in a rasagiline-treated subject was anemia (rasagiline 0.3%,

n=1; placebo n=0). In Cohort 9 (all PD patients exposed to rasagiline), anemia (0.2%, n=3) and myeloma (0.1%, n=1) were the only two AEs resulting in discontinuation.

AEs: No hematologic or lymphatic AEs were experienced by at least 1% of rasagiline-treated subjects in Cohort 1. For Cohort 2, AEs reported for 1% or more of rasagiline (1 mg)-treated subjects were anemia (rasagiline 1.3%, n=5; placebo 1.0%, n=4) and ecchymosis (rasagiline 1.1%, n=4; placebo 0.8%, n=3.) Hematologic or lymphatic AEs occurring in 1% or more of all Parkinson's disease patients exposed to rasagiline (Cohort 9) were anemia (2.3%), ecchymosis (2.1%) and leukopenia (1.0%).

Laboratory Data: The sponsor states there was a higher frequency of shift from high/normal to low values for rasagiline 1 mg compared to placebo for hemoglobin (2.7% [rasagiline] versus 1.3% [placebo]), hematocrit (3.4% versus 1.3%), white blood cells (4.7% versus 2.6%), and neutrophils (6.8% versus 1.4%). Teva writes that (ISS 7.2.1). When PCS thresholds were used, however, there was no important difference between the treatment groups, and a dose response was not demonstrated for any parameter. The sponsor notes that the increased shift from high/normal to low neutrophils in rasagiline 1 mg monotherapy was not seen with rasagiline adjunct therapy. Finally, there was no substantial excess of AEs consistent with hematological toxicity observed in rasagiline treated patients compared to placebo patients.

6.12 Special Senses Disorders

(includes Hearing and Vestibular Disorders, Special Senses other, and Vision Disorders)

Deaths: No rasagiline-treated subjects who died had a special senses event listed as a cause of death.

SAEs: No special senses SAEs were reported for Cohort 1 (monotherapy), Cohort 2 (levodopa adjunct) or Cohort 9 (all PD subjects exposed to rasagiline).

Discontinuations: No rasagiline-treated participants in Cohort 1 discontinued due to a special senses AE. For Cohort 2, a single rasagiline-treated subject discontinued due to eye disorder (0.3%), compared to none in placebo. In Cohort 9 (all PD patients exposed to rasagiline), special senses AE lead to the discontinuation of one subject each for eye disorder and retinal disorder.

AEs: In Cohort 1, cataract (rasagiline n=4, 1.4%; placebo n=2, 1.3%), conjunctivitis (rasagiline 1.7%, n=5; placebo 0.7%, n=1), dry eyes (rasagiline 1.7%, n=5; placebo 1.3%, n=2), and tinnitus (rasagiline 1.0%, n=3; placebo 0.7%, n=1) were the only AEs affecting more than 1% of rasagiline-treated subjects. For Cohort 2, abnormal vision (rasagiline 1.6%, n=6; placebo 0.5%, n=2) was the only AE occurring in more than 1% of rasagiline subjects. In Cohort 9 (all PD patients exposed to rasagiline), special senses AEs affecting at least 1% of subjects were abnormal vision (2.1%), cataract specified (1.6%), conjunctivitis (1.3%) and tinnitus (1.0%).

6.13 Endocrine

Deaths: No rasagiline-treated subject who died had an endocrine disorder listed as a cause of death.

SAEs: No endocrine SAEs were reported for the two placebo-controlled cohorts. For Cohort 9 (all PD patients exposed to rasagiline), the only SAEs reported were ADH inappropriate (n=2, 0.2%) and diabetes mellitus (n=1, 0.1%).

Discontinuations: No rasagiline-treated subjects in either of the placebo-controlled cohort discontinued due to an endocrine AE. In Cohort 9 (all PD patients exposed to rasagiline), one subject each discontinued due to ADH inappropriate and hyperthyroidism.

AEs: In the placebo-controlled cohorts and Cohort 9, no endocrine AEs occurred more than 1% of subjects exposed to rasagiline.

Laboratory Data: In Cohort 1, there was an increased percentage of subjects in the rasagiline 1 mg group compared to placebo who experienced a baseline to LOV shift from low/normal to high glucose (10.1 [rasagiline] versus 4.7 [placebo]). However, there was no difference between the treatment groups when the PCS thresholds were utilized. Additionally, no excess of a shift from low/normal to high glucose was observed in the rasagiline 1 mg group in Cohort 2. Finally, there was no substantial excess of AEs consistent with glucose dysregulation observed in rasagiline treated patients compared to placebo patients.

6.14 Body as a Whole

Deaths: Teva reported two Body as a Whole category deaths (sudden death) in rasagiline-treated subjects. These were likely cardiac in nature¹⁴⁷, although this could not be verified due to the circumstances of death. Five additional subjects were classified as cause of death “Unknown¹⁴⁸” (n=3) and “Complex¹⁴⁹” (n=2).

SAEs: No Body as a Whole SAEs were reported for at least 1% of rasagiline-treated subjects in Cohort 1, Cohort 2, or Cohort 9. For Cohort 1, the only Body as a Whole SAE reported for more than one subjects was abdominal pain (rasagiline 0.7%, n=2; placebo n=0). In Cohort 2 (levodopa adjunct), the only SAE experienced by more than one rasagiline (1 mg)-treated subject was accidental injury (rasagiline 0.8%, n=3; placebo

¹⁴⁷ These deaths are included in the CV section of the ROS within this review. The other “unknown” death occurred in a subject who had discontinued five months earlier due to a paranoid disorder, and no details of his death were available.

¹⁴⁸ One of these deaths, in which a participant was found dead in an overheated apartment, was discussed in the CV section of the ROS.

¹⁴⁹ As pneumonia, pulmonary embolism, urinary tract infection and bowel obstruction were contributory factors in these deaths, they are mentioned in the ROS section of the Respiratory System, Urologic System and Gastrointestinal System, respectively.

0.8%, n=3). In Cohort 9 (all PD patients exposed to rasagiline), SAEs reported for more than one subject were accidental injury (0.5%), abdominal pain (0.4%), headache (0.4%), asthenia (0.3%), fever (0.3%), chest pain (0.2%) and infection (0.1%).

Discontinuations: No Body as a Whole category AEs led to discontinuation of at least 1% of rasagiline subjects in either the placebo-controlled cohorts or Cohort 9 (all PD patients exposed to rasagiline).

AEs: For Cohort 1, AEs occurring in 1% or more of rasagiline-treated subjects, and which were more frequent than in placebo subjects, were: headache (rasagiline 13.9%, n=41; placebo 11.9%, n=18), back pain (rasagiline 5.4%, n=16; placebo 5.3%, n=8), flu syndrome (rasagiline 4.4%, n=13; placebo 0.7%, n=1), fever (rasagiline 2.7%, n=8; placebo 1.3%, n=3), neck pain (rasagiline 1.7%, n=5; placebo n=0), neoplasm (rasagiline 1.0%, n=3; placebo n=0), and allergic reaction (rasagiline 1.0%, n=3; placebo 0.7%, n=1).

In Cohort 2, AEs meeting the same criteria as described above for Cohort 1 included accidental injury (rasagiline 8.2%, n=31; placebo 5.2%, n=20), abdominal pain (rasagiline 3.9%, n=15; placebo 1.3%, n=5), pain (rasagiline 3.7%, n=14; placebo 3.4%, n=13), flu syndrome (rasagiline 1.1%, n=4; placebo 0.5%, n=2), hernia (rasagiline 1.3%, n=5; placebo 0.8%, n=3), and neck pain (rasagiline 1.6%, n=6; placebo 0.5%, n=2).

For Cohort 9 (all PD patients exposed to rasagiline), AEs reported by 1% or more of subjects were infection (17.7%), accidental injury (17.6%), headache (10.3%), back pain (9.9%), pain (9.9%), asthenia (7.4%), abdominal pain (5.4%), chest pain (4.2%), neck pain (2.6%), hernia (2.4%), infection fungal (2.1%), allergic reaction (1.3%), fever (2.1%), surgery/procedures (1.5%) cellulitis (1.3%) and neoplasm (1.0%).

7. Discussion

Adverse Event Monitoring

Teva adequately captured and described safety data during the rasagiline development program. The three Phase III trials (TEMPO, LARGO and PRESTO) appeared to have been appropriately designed to capture treatment emergent adverse events and other safety data. The coding of adverse events was generally acceptable, although the FDA did request that the sponsor make several adjustments in how certain classes of adverse events were coded. The most notable of these adjustments was that fall-related verbatim adverse events be coded to both a new preferred term (PT) "FALLS" and, when fall-related verbatim terms included two or more events, to a reasonable PT for the precipitant or resultant verbatim term. Following these revisions, the coding process provided an accurate depiction of rasagiline's adverse event profile.

Exposure

The overall number of subjects exposed to rasagiline at any dose (including 1537 Parkinson's disease patients) just exceeded ICH guidelines. The three phase III trials each included a rasagiline 1 mg/day treatment arm, which is the dosage that Teva intends

to recommend for the treatment of Parkinson's disease. The number of subjects exposed to this indicated dose at six months and one year also met ICH recommendations. As with most NDA safety databases, due to the relatively small number of persons exposed, there was limited power to detect infrequent drug-related events.

The age distribution of subjects in the different treatment groups within the two placebo-controlled cohorts (monotherapy and levodopa adjunct) was similar. When the age distribution of the two placebo-controlled cohorts were compared to one another, subjects in Cohort 2 were slightly older (mean age 64.2 years) than those in Cohort 1 (mean age 61.3 years) which could be expected given that subjects in Cohort 2 (levodopa adjunct treatment) had more advanced Parkinson's disease. The age mean, median and range were likewise equivalent between treatment groups within the three Phase III trials. When adverse event risk was stratified by age greater or less than 65 years, no meaningful differences in risk were observed.

For the 1537 Parkinson's disease patients exposed to rasagiline (Cohort 9), there was an overall male predominance (64.4%). A roughly equivalent percentage (~33%) of rasagiline and placebo group subjects in Cohort 1 and Cohort 2 were female. No significant difference in adverse event risk was associated with a particular gender.

For Cohort 2 (placebo-controlled levodopa adjunct), Teva also stratified data by concomitant medications, including dopamine agonists, amantadine, entacapone and antidepressants. The use of the latter (antidepressants) was significantly restricted by the study protocol, due to serious adverse events associated with concomitant use with other MAO inhibitors. The most notable finding upon stratification was that rash (n= 10), skin disorders (n=5), tenosynovitis (n=5) and extrapyramidal syndrome (n= 10) were reported in the rasagiline treatment group only in participants receiving concomitant dopamine agonists. In addition, hallucinations and peripheral edema were seen primarily with combined dopamine agonist and rasagiline treatment.

There were no cases of pregnancy or rasagiline overdose in patients receiving rasagiline during the development program.

Deaths

A total of twenty-one rasagiline-treated subjects, five entacapone-treated subjects and six placebo subjects died during the rasagiline development program. The reported causes of death were those expected in an older population. Six rasagiline-treated subjects, compared to no placebo or entacapone-treated subjects, died of cerebrovascular accidents. However, rates of non-fatal cerebrovascular accidents were similar in the two placebo-controlled cohorts. The rasagiline development database included none of the following causes of death: acute hepatic failure, acute renal failure, serious skin reactions, rhabdomyolysis, pancreatitis or hematological dyscrasias.

Serious Adverse Events (SAEs)

In general, rasagiline and placebo subjects had similar SAE risks. No specific SAEs were reported for more than 2% of participants in Cohort 9 (all Parkinson's disease patients

exposed to rasagiline). SAEs reported by at least 1% of Cohort 9 subjects were accidental injury (1.9%), skin melanoma (1%) and angina pectoris (1%). In the primary data trials, there were no SAEs of liver failure, acute renal failure, aplastic anemia, serious skin reactions, or pancreatitis. Two SAEs of rhabdomyolysis were reported in ongoing studies, both following a fall and prolonged immobilization. One case lacked laboratory values (creatinine phosphokinase) confirming rhabdomyolysis.

SAE: Melanoma

Sixteen cases of melanoma were diagnosed among fifteen rasagiline-treated subjects, and one placebo-treated subject.¹⁵⁰ An additional three melanomas were identified prior to treatment initiation. A number of factors complicated the analysis of melanoma within the rasagiline development program. The most significant of these was that most of the cases were diagnosed in extension studies without parallel controls, and that the majority (14 of 20) were identified following the implementation of active skin examinations to screen for melanomas in all rasagiline trials. Other confounding factors include the presence of concomitant Parkinson's disease and other medications (especially levodopa), the variable melanoma risk factors among patients, the different background rates for the geographic locations of the study sites, and the rapidly increasing rates of melanoma worldwide.

When the number of cases of invasive melanoma (seven cases) in North American rasagiline-treated subjects was compared to the number of invasive melanomas expected by age-adjusted rates with the Surveillance, Epidemiology, and End Results (SEER) registry of the U.S. National Cancer Institute, the number of cases observed was significantly higher than expected. This remained true even when the number of cases expected by SEER rates was tripled to adjust for any potential under-reporting (Incidence Density Ratio: 3.0, 95% CI 1.3, 5.8).

To address the effect of the active screening for melanoma on the number of melanoma cases uncovered, comparison was also made with another population undergoing melanoma screening through the American Academy of Dermatology (AAD) skin cancer screening program. Although the number of *invasive* melanomas did not differ significantly from those expected by age-adjusted rates from the AAD screening program (Incidence Density Ratio: 2.6, 95% Confidence Interval: 0.72, 6.74), the number of *in situ* melanomas was significantly increased (Incidence Density Ratio: 10.2, 95% Confidence Interval: 3.7, 22.1).

The rate of melanomas within the rasagiline development program fell within the range of rates for five other Parkinson's disease therapy programs. It was exceeded by melanoma rate within in the tolcapone development program.

While some analyses and other considerations of the data accumulated during the rasagiline development program are not supportive of a causal association between rasagiline and melanoma, others do suggest an elevated risk. However, these analyses are limited by the lack of a parallel control group with comparable demographics and

¹⁵⁰ One rasagiline-treated subjects experienced two melanomas.

Parkinson's disease history. It is therefore recommended that, as part of a Phase IV commitment, Teva conduct a randomized controlled trial to assess melanoma rates in Parkinson's disease patients who are exposed or not exposed to rasagiline.

Potential SAE: Tyramine Reaction

The co-administration of MAO inhibitors and tyramine (which is contained in a variety of foods such as aged cheese and red wine) may result in a hypertensive crisis (also known as a "cheese effect.") The sponsor studies specifically investigating the potential for hypertensive crisis resulting from interaction of rasagiline with tyramine administration is addressed by Dr. Len Kapcala in his review.

Safety data was generally not suggestive of the presence of tyramine reactions with the dosages of rasagiline used in the Phase III studies. Specifically, no deaths were attributed to hypertensive reactions. In the placebo-controlled cohorts, no excess of discontinuations due to hypertension was seen among the rasagiline-treated subjects compared to placebo-treated subjects. Vital sign monitoring likewise did not register hypertension more frequently in the rasagiline-treated subjects. In Cohort 9, hypertension was reported as a serious adverse event in only 0.5% of subjects (n=7).

A possible exception to this lack of evidence for tyramine reactions is a previously normotensive¹⁵¹ Phase I/II subject who experienced an unexplained hypertensive crisis that resulted in her discontinuation from the study.¹⁵² No mention was made of the tyramine content of the subject's recent diet in the study report or in the case report form, and a tyramine reaction cannot be excluded.

Discontinuations

Overall, 9.4% of rasagiline-treated subjects discontinued the development program early due to adverse event. In the placebo-controlled monotherapy cohort, the rate of discontinuation was higher in rasagiline-treated subjects (7.8/100 PYs) than in placebo subjects (1.5/100 PYs). The most frequently reported AE leading to discontinuation in rasagiline subjects was hallucinations (1.3% [n=2] rasagiline 1 mg; 0% placebo). In the placebo-controlled levodopa adjunct cohort, rasagiline subjects (11/100 PYs) and placebo subjects (13/100 PYs) discontinued early due to AE at a similar rate. AEs reported by more than one discontinuing rasagiline-treated subject, and which were more frequent than in placebo subjects, were hallucinations, postural hypotension, abdominal pain and dyspnea. None of these adverse events were more than twice as common in the rasagiline group as the placebo group. In Cohort 9 (all Parkinson's disease patients exposed to rasagiline), the only AE leading to early discontinuation in 1% or more of subjects was hallucinations (1%).

The sponsor stated that in approximately 7% of discontinuations they were unable to attribute the discontinuation to a particular AE. In such cases they did not include the AE data for that subject in the data tables for discontinuations, although they did discuss these discontinuing subjects in the corresponding text sections of the NDA. It is

¹⁵¹ This subject was normotensive during her prior study monitoring before the hypertensive episode.

¹⁵² Information on this subject (TVP-1012/111 #808) is included on page 36 of this review.

recommended that the sponsor should take additional measures to identify the AEs associated with discontinuation. This may include evaluating a listing of all AEs reported by discontinuing subjects along with the dates of their AEs and discontinuation.

Adverse Events

Following the re-coding described above, the most common adverse events (defined by the sponsor as those occurring in 2% or more of the rasagiline 1 mg group and numerically at least twice as frequent than in the placebo group) for rasagiline monotherapy were¹⁵³ flu syndrome, depression, rhinitis, conjunctivitis, fever, malaise, neck pain, neoplasm, arthritis, vertigo, ecchymosis, gastroenteritis, and infection.

The most common adverse events for rasagiline as levodopa adjunct were postural hypotension, accidental injury, constipation, weight loss, abdominal pain, vomiting, dystonia, anorexia and abnormal dreams.

There is a substantial excess of flu-syndrome, arthralgia and fever in rasagiline-treated subjects compared to placebo, most notably in the rasagiline monotherapy cohort. In cohort 1, 4.7%¹⁵⁴ of rasagiline-treated subjects reported flu syndrome, compared to 0.7% in placebo-treated subjects: a 6.7-fold excess in the rasagiline treatment group. Within the NDA the sponsor does not provide analysis or commentary on this potential safety signal beyond describing it. The sponsor should present additional analysis exploring the nature of this potential syndrome. These analyses may include the following: creation of a case definition, reassessment of verbatim adverse events to ascertain which meet the case definition, time to onset, trends in associations with other adverse events, concomitant medication (especially amantadine) and examination of these adverse events over time.

Vital Signs and Laboratory Data

With the exception of postural hypotension, no important trends in the vital sign or laboratory data was observed in rasagiline-treated subjects compared to placebo-treated subjects. Postural hypotension was observed in a higher percentage of rasagiline-treated subjects than placebo subjects, especially in the levodopa adjunct cohort (rasagiline 3.2%, placebo 1.3%).

ECG

The data presented for rasagiline monotherapy (Cohort 1) was limited to the point that additional analyses are necessary in order to reach conclusions on the effect of rasagiline monotherapy on ECG parameters, including QTc interval. The ECG data from Phase I/II studies was also lacking.

¹⁵³ The most common AEs for both rasagiline monotherapy and rasagiline as levodopa adjunct given in this section of the review are listed in order of descending percentage of rasagiline-treated subjects.

¹⁵⁴ The 4.7% flu syndrome in rasagiline-treated subjects represents the percent following the FDA-requested revision of the coding of certain verbatim terms, and was submitted with the 120 Day Safety Update. In the initial NDA submission, 6.0% of rasagiline-treated Cohort 1 subjects were reported flu syndrome, but a number of these were cases of gastroenteritis inappropriately classified as flu from the verbatim term "stomach flu."

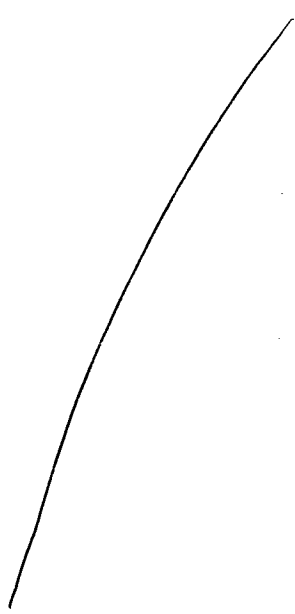
The sponsor states that because ECG analysis in the Cohort 1 study TEMPO consisted solely of classifying ECGs as normal or abnormal (without collecting data on the nature of the abnormality or ECG intervals), additional data is not immediately available. It is presumed that the sponsor has retained the original ECG tracings from TEMPO, and it is recommended that these be re-read in a method similar to the sponsor analysis of ECG data for the levodopa adjunct studies. This may include having the ECGs assessed by a centralized facility and more detailed assessment of the QT interval.

However, Teva's more detailed analyses of ECG data for the two levodopa adjunct studies did not suggest rasagiline-related QT prolongation or other cardiac abnormalities.

Recommendations for the Proposed Labeling

It is recommended that the following statement regarding the occurrence of melanoma be included in the — the labeling:

Melanoma



This reviewer requested that some preferred terms within the initially submitted AE Coding Dictionary be re-coded. As a result of this re-coding there was some shifting of preferred terms meeting or not meeting criteria for "common" and "most common" AEs. Specifically, for the rasagiline monotherapy placebo-controlled cohort, the new preferred term "Falls" meets the criteria for common AEs, while ecchymosis, gastroenteritis, and

infection would meet criteria for “most common.” In the placebo-controlled rasagiline as levodopa adjunct cohort, ecchymosis, falls and colds were classified as common AEs, while accidental injury was reclassified from “common” to “most common” and arthralgia from “most common” to “common.” The tables of treatment emergent AEs in the proposed labeling should be revised to reflect these changes.

There was a significantly higher rate of AE reporting in the levodopa adjunct North American study PRESTO (in which 90% of subjects reported AEs) than in the Non-North American study LARGO (in which 50% of subjects reported AEs). Although this discrepancy in AEs was somewhat less when only serious adverse events were compared, it nevertheless remained. The sponsor suggests these differences may be due to cultural variations, however it would seem that serious adverse events should not greatly influenced by potential cultural differences among study populations.

Given this substantial difference, it is recommended that in the labeling the levodopa adjunct safety data be restricted to that from the North American study PRESTO only, and not be presented as pooled data with LARGO.

Postural hypotension was a common adverse event, especially when rasagiline was used as an adjunct to levodopa. A statement noting this should be made prominent within the labeling.

In the proposed labeling Teva notes that significant adverse events have been reported with the use of MAO inhibitors and various concomitant medications. In contrast to the selegiline labeling, the rasagiline proposed labeling does not state specifically what these events were. More detailed information on the nature of the significant adverse events referred to in the rasagiline proposed labeling should be provided.

The sponsor statements regarding concomitant use of antidepressants and rasagiline during the development program should specifically acknowledge the restrictions on antidepressant usage within the trials and the exact number of subjects to whom rasagiline and antidepressants were co-administered.

Although overdose has not yet been observed with rasagiline, based upon experience with other selective MAO inhibitors more specific information on the expected symptoms and general treatment should be provided

15 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

HOW SUPPLIED

AGILECT 1 mg are white to off-white, round, flat, beveled tablets, debossed with "GIL 1" on one side and plain on the other.

Supplied as follows:

Bottles of 30 tablets NDC XXX

[NDC (National Drug Code)]

Storage: Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

Rx only

Manufactured by:

Teva Pharmaceutical Industries Ltd.
Kfar Saba 44102, Israel

Marketed by:

Teva Neuroscience, Inc.
Kansas City, MO 64131

And

Eisai Inc.
Teaneck, NJ 07666

Revision 08/03

9. Attachments

9.1 Summary of Studies in the Rasagiline NDA

Abbreviations: BA-bioavailability, LD-levodopa, PK-pharmacokinetics, PD-Parkinson's disease, BE-Bioequivalence, Pts-Patients

Completed Studies				
Study Number	Type	Description	# Subjects Entered/Completing	Treatment Length
TVP-1012/423	BA	Randomized, open label, two-way cross-over study of 2 mg (oral & IV) in healthy males	14/14	Single Dose
TVP-1012/421	BA	Open, two-way, cross-	19/18	Single

		over of 2 mg healthy males		Dose
TVP-1012/427	BA/BE	Open, randomized cross-over of 1 mg in healthy subjects	24/22	Single Dose
CC547	PK	Double-blind, randomized, placebo-controlled of increasing 1, 2, 5, 10 and 20 mg in healthy males	14/12	Single Dose
CD596	PK	Double-blind, randomized of increasing 2,5 and 10 mg in healthy males	24/24	10 days
TVP-1012/422	PK	Open label, single dose of ¹⁴ C-radiolabelled 2 mg equivalent in healthy males	8/8	Single dose
TVP-1012/231	PK	Multi-center, double-blind, randomized, placebo-controlled of 1, 2 and 4 mg in PD pts. not treated with LD	56/55	10 weeks
TVP-1012/111	PK	Double-blind, randomized, placebo-controlled of 1, 2, 5 and 10 mg in PD pts. treated with LD	10/6	8 weeks
TVP-1012/121	PK	Double-blind, randomized, placebo-controlled of 1 and 2 mg in PD pts. treated with LD	5/5	8 weeks
TVP-1012/112	PK	Double-blind, randomized, placebo-controlled of 0.5, 1 and 2 mg in PD pts. treated with LD	70/64	12 weeks
TVP-1012/424	Intrinsic Factor PK	Open, active control, multiple dose of 1 mg in healthy subjects and subjects with mild to moderate hepatic impairment	25/24	7 days
TVP-1012/425	Intrinsic Factor PK	Open, active control, parallel group of 1 mg	24/24	7days

		in healthy subjects and subjects with mild to moderate hepatic impairment		
TVP-1012/426	Extrinsic Factor PK	Open, multiple dose of 1 mg rasagiline with concomitant ciprofloxacin in healthy males	13/13	13 days
TVP-1012/430	Extrinsic Factor PK	Double-blind, multiple dose of 1 mg rasagiline with concomitant theophylline in healthy subjects	25/23	25 days
P94159	Tyramine Interaction	Placebo run-in followed by double-blind, randomized, placebo-controlled multiple dose study of 1 and 2 mg rasagiline x 10 days, or selegiline x 10 days, plus tyramine, in healthy subjects	30/27	10 days
TVP-1012/132	Tyramine Interaction	Double-blind, placebo-controlled, randomized study of 1 and 2 mg rasagiline with escalating tryramine in PD pts. treated with LD	20/18	10 weeks

		3: Placebo x 18 weeks Total	687/599	
TVP-1012/133 (PRESTO)	Safety and Efficacy, Population PK	Multi-center, double-blind, randomized, placebo-controlled study in PD pts. treated with LD 1. 0.5 mg qd x 26 weeks 2. 1 mg qd x 26 weeks 3. Placebo x 26 weeks Total	164/142 149/132 159/140 472/414	26 weeks
TVP-1012/133a (PRESTO Sub-study)	Tyramine Interaction	Single 50 mg dose tyramine on last dosing day of 26 weeks	55/55	Single dose Tyramine
TVP/1012/311	Special Population: Alzheimer's Disease	Multi-center, double-blind, randomized, placebo-controlled study of 1, 2 or 4 mg rasagiline in Alzheimer's disease pts. 1: 1 mg qd x 8 weeks 2: 1 mg qd x 1 week, then 2 mg x 7 weeks 3: Escalating to 4 mg 4: Placebo Total:	11/10 12/8 11/6 13/9 47/33	8 weeks
Ongoing Studies at time of NDA Submission				
TVP-1012/123 (LARGO Extension)	Safety & Efficacy	Multi-center, double-blind, double-dummy, randomized active extension of	480/194 (223 ongoing)	9 months

		LARGO (TVP-1012/122)		
TVP-1012/135 (PRESTO Extension)	Safety & Efficacy	Multi-center, double-blind, randomized, active extension of PRESTO (TVP-1012/133)	388/155 (147 ongoing)	6 months
TVP-1012/233 (TEMPO Extension)	Safety & Efficacy	Open-label extension of TEMPO (TVP-1012/232)	306/224 ongoing	Until product launch (ongoing for ~ 3 years)
TVP-1012/113	Safety & Efficacy	Open extension of TVP-1012/112	44/5 (11 ongoing)	“Until approval” (ongoing for ~ 6 years)

9.2 Summaries of Death Narratives for Rasagiline-Treated Participants

(Presented in same order as FDA Table 14 and condensed from the study narratives supplied by Teva)

Cerebrovascular Accidents

PRESTO #40: This 73 year-old man received his first dose of rasagiline (1 mg/day) on [redacted]. His significant past medical history included PD, stroke, hypertension, chronic bronchitis, cirrhosis, atherosclerosis, paroxysmal supraventricular tachycardia, minimal cardiomegaly, sleep apnea, gastroesophageal reflux disease (GERD) and depression. His concomitant medications were pramipexole, entacapone, sertraline, esomeprazole magnesium, hydrocodone, celecoxib, sildenafil, guaifenesin, zaleplon, zolpidem and tolterodine.

On [redacted] the participant was hospitalized with the diagnosis of stroke. He was discharged to his home, and died on [redacted]. The date of the last dose of the study drug was estimated to be [redacted] (study day 99). The cause of death given on the death certificate was brainstem infarction and arteriosclerosis. No autopsy was performed. Other adverse events reported during the study period included dyskinesia and a gum infection ([redacted]).

PRESTO #93: This 77 year-old man received his first dose of rasagiline (0.5 mg/day) on [redacted]. His significant past medical history included coronary artery disease, hypertension, osteoporosis, GERD, actinic keratosis, and removal of pre-cancerous lesion from scalp (1995). His concomitant medications were amlodipine, lansoprazole, metoprolol, isosorbide and acetylsalicylic acid.

On March 8, 2002, the participant reported increased falls. From March 11 until April 8, 2002 the subject experienced moderate confusion, and the study drug was discontinued from March 19 until April 1, 2002. On _____ (study day 158) he experienced acute onset of involuntary movements in his left arm and leg. The diagnosis of stroke was confirmed on MRI. The study drug was permanently stopped at this time. The subject was discharged to a rehabilitation nursing facility, but by _____ had developed pneumonia and stopped eating. He died of a reported cardiac arrest on _____
— The narrative makes no mention of death certificate determination or autopsy.

TVP-1012/123 (LARGO Extension) #15826: This 76 year-old man received his first dose of rasagiline (1 mg/day) on _____. Significant past medical history included PD, ischemic heart disease and congenital hip dysplasia. Concomitant medications were levodopa/carbidopa, bromocriptine, and levodopa/benserazide.

On _____ (46 days after study start) the participant was hospitalized following sudden speech difficulties and right hemiparesis. A brain CT demonstrated diffuse lacunar infarcts mainly in the right basal ganglia and capsule bilaterally, as well as a lesion in the left capsular-thalamic region. The study drug was stopped on _____ (study drug date 46). The patient was discharged home and his condition was reported as stable. The participant died in his home on _____. The official cause of death in the narrative was stated to be stroke, and an autopsy was not performed.

TVP-1012/233 (TEMPO Ext.) #435: This 76 year-old woman received her first dose of rasagiline on _____. She had initially taken 2 mg/day, but had been changed to 1 mg/day on August 4, 2000. Her past medical history was significant for PD, coronary artery disease, chronic obstructive pulmonary disease, hypertension and osteoarthritis. Concomitant medications were not listed.

On _____ she complained of right-sided pain and weakness in her left arm. She developed left hemiparesis and was diagnosed with stroke, although CT scan was stated to reveal no new infarct or hemorrhage. Due to her multiple medical problems she was not considered a candidate for rehabilitation, and was transferred to a long-term care facility. There her course was described as “gradually downhill” with generalized atherosclerosis, increased hip pain, renal failure, and worsening obstructive pulmonary disease. The study investigator was informed that the patient died of a stroke on _____ (study drug day 1264). The narrative stated that no other information regarding the death was available.

TVP-1012/233 (TEMPO Ext.) #150: This 61 year-old woman was enrolled in TVP-1012/233 on _____, initially receiving rasagiline 2 mg/day, then 1mg/day beginning July 15, 2000. Her past medical history included PD and hypertension. Her concomitant medications were not listed in the death narrative. The sponsor reports that during the study her ECG and vital signs measurements were within normal range.

The participant was hospitalized on _____ (study day 1551), following a two-day history of speech difficulties, followed by headaches, unresponsiveness and two generalized tonic-clonic seizures on the day of admission. An initial brain CT was unremarkable, but a repeat scan on _____ revealed a left temporal-parietal non-hemorrhagic stroke. The possibility of CNS infection and vasculitis were reported to have been considered and excluded. On _____ the patient had developed shortness of breath, believed secondary to pneumonia, and renal insufficiency. She remained unresponsive and ventilator-dependent during her hospital course, although the seizures did not recur. She died on _____ and the sponsor narrative characterized her death as resulting from the initial cerebrovascular accident. No autopsy or death certificate information was noted in the death narrative.

TVP-1012/135A (PRESTO Open Label Ext.) #639: This 52 year-old woman received her first dose of rasagiline (initial dose 0.5 mg, beginning 1 mg in the open-label extension) on _____. Her significant past medical history included PD, temporomandibular joint dysfunction, headaches, neck dystonia, mitral and tricuspid regurgitation (2001), and depression. Her concomitant medications were levodopa/carbidopa, lorazepam, paroxetine, paracetamol, calcium carbonate, amantadine, entacapone and botulinum toxin.

The subject's vital signs were reported as normal throughout the double blind active extension phase and open-label extension. On _____ (495 days after first rasagiline dose) the patient was hospitalized due to a CVA with right basal ganglion hemorrhage, confirmed by CT scan. The next day the hemorrhage worsened and she underwent craniotomy. She was extubated on _____ but developed pneumonia and was re-intubated on _____. The patient died on _____. No autopsy was performed.

Sudden Deaths

TVP-1012/135 (PRESTO Ext.) #125: This 68 year-old man received his first dose of rasagiline (0.5 mg) on _____. His past medical history was significant for PD, exertional chest pain (cardiac evaluation reported as negative), insomnia and benign hallucinations. Concomitant medications were carbidopa/levodopa, pramipexole, pravastatin, lorazepam, and warfarin.

On _____, the participant was found dead while snorkeling on vacation (study day 588). He was discovered to be unresponsive by his wife, and was transferred to the hospital by helicopter where he expired. Findings from autopsy were reported as "cardiomegaly with dilatation of the left atrium and ventricle, severe narrowing of the coronary arteries caused by atherosclerosis and intact surgical repair to atrial septal wall." Causes of death listed on the death certificate were cardiac failure with severe narrowing of coronary arteries and coronary artery atherosclerosis. ECG performed for the core study screening visit was stated to demonstrate first degree heart block and sinus bradycardia. The subject's core study termination ECG was reported as normal

TVP-1012/311 #349: This 78 year-old man received his first dose of rasagiline (escalating up to 3 mg/day) on [redacted]. His past medical history was significant for PD and Alzheimer's disease. He received no concomitant medications.

On [redacted] (35 days after study start) the participant died at his home during the night. He had complained of bilateral arm pain the evening before. His last meal, as reported by his family, was considered to be of low-tyramine content. He had a history of heavy smoking, but normal blood pressure during study monitoring.

Ruptured Aneurysm

TVP-1012/233 (TEMPO Ext.) #68: This 75 year-old man received his first dose of rasagiline on [redacted]. He had initially taken 2 mg/day, but had been changed to 1 mg/day on June 1, 2000. His past medical history was significant for Parkinson's disease (PD), hypertension and hypercholesterolemia. His concomitant medications were pramipexole, furosemide, diltiazem, aspirin, and atenolol.

On study drug day 1409 [redacted], he was admitted to the hospital with complaints of back pain. CT scan revealed a large thoracic aneurysm, judged to be inoperable. He lapsed into unconsciousness later that evening and died the next day due to rupture of the aneurysm.

Pneumonia

LARGO #16415: This 71 year-old women received her first dose of rasagiline (1 mg/day) on [redacted]. Her past medical history included PD, diabetes mellitus, depression and hypercholesterolemia. Her concomitant medications were levodopa/benserazide, glibenclamide, and alprazolam.

The participant noted symptoms of bronchitis on [redacted] and was treated by her family physician. Shortly thereafter she missed her study termination visit due to being hospitalized for respiratory difficulty. It was suggested in the sponsor's narrative that this may have been due to bronchial aspiration, as onset occurred after drinking a cup of tea. Chest x-ray revealed bilateral infiltrates, and she improved with oxygen administration. Teva reported that the study investigator requested she discontinue her study medication, but it apparently continued. Her hospital course included treatment for a sacral decubitus, and episodes of hypotension, leg swelling, elevated blood glucose and hypokalemia. On [redacted] (study day 144) she was reported to be difficult to arouse, and she subsequently died of a suspected cardiac arrest. The narrative makes no mention of death certificate determination or autopsy.

TVP-1012/135 (PRESTO Ext.) # 601: This 80 year-old woman received her first dose of rasagiline (0.5 mg) on [redacted]. He past medical history was significant for PD, mild congestive heart failure (seen on core study screening x-ray), gastroesophageal reflux, depression, anxiety, and hallucinations. Concomitant medications were

carbidopa/levodopa, pramipexole, lansoprazole, amitriptylline, bisacodyl, calcium carbonate, torasemide, spironolactone and clonazepam.

On [redacted] (study drug day 89), the participant was unresponsive and hospitalized with suspected pneumonia. She subsequently experienced a pulmonary embolism and required intubation. All medications, including the study drug, were reported to have been discontinued upon admission, although levodopa/carbidopa was restarted after 3 to 5 days. Her condition improved and she was extubated, but continued to have chronic respiratory failure. She was discharged to home hospice care, and died on [redacted]. The cause of death was listed as Parkinson's disease, although the narrative does not note that this was specifically stated on the death certificate.

Cancer

TVP-1012/123 (LARGO Extension) #15602: This 64 year-old man received his first dose of rasagiline (1 mg/day) on [redacted]. His significant past medical history included PD, prostatectomy for adenocarcinoma, cerebrovascular lacunae, and first degree AV block. His concomitant medications were levodopa/carbidopa, pramipexole, amantadine, biperidine, estradurin, alprazolam, and carbamazepine.

During a termination visit on January 23, 2003, the participant reported a 3-week history of general weakness, loss of appetite, nausea and dizziness. He was referred for abdominal ultrasound which revealed hepatic metastases. Gastric biopsy demonstrated malignant gastric lymphoma (MALT lymphoma) approximately 401 days after study start. The patient was discharged to his home and died on [redacted].

TVP-1012/233 (TEMPO Extension) # 164: This 76 year-old man received his first dose of rasagiline (2 mg/day) on [redacted], switching to 1 mg/day in the extension study on September 22, 2000. His past medical history is significant for PD, seasonal allergies, and arthritis. His concomitant medications were levodopa/carbidopa (started February 2000), Naprosyn, Inderal, aspirin, Dramamine, and Lodosyn.

In [redacted] (approximately 75 days after study start) the participant was diagnosed with a malignant melanoma on his forehead. The subject was reported to have entered the trial with a suspicious lesion on his forehead for one year. Pathology determined the melanoma to be nodular type, Clark's level IV. Melanoma risk factors listed were: adulthood, Caucasian race, blue eyes, fair complexion, freckles, sun sensitivity, inability to tan, severe sunburns in childhood, and one or more irregularly pigmented lesions.

Approximately two years later, while in the open-label extension portion of the trial, the participant noted enlarged lymph nodes. Aspiration confirmed metastatic melanoma, and the patient underwent lymph node dissection. A complete resection of a squamous cell carcinoma on his right arm was also performed. The participant began radiotherapy. Three months later a surgical excision of a recurrent melanoma on his forehead was

performed. The participant terminated from the study in _____ (approximately study drug day 673), and subsequently died of progressive metastatic melanoma.

TVP-1012/Compassionate Use #50110: This 77 year-old man received his first dose of rasagiline (1 mg) on _____. His past medical history was notable for prostatectomy (1993) and ongoing prostatic hypertrophy with permanent catheter (inserted _____), diabetes mellitus, polyneuropathy and normocytic anemia. Concomitant medications included: levodopa/carbidopa, amantadine, pergolide, glibenclamide and alfuzosin.

The subject was hospitalized on _____ (146 days after study start), due to fever, chills and anemia. High levels of alkaline phosphatase, LDH and PSA initially found during the active extension study were persistent. Hemoglobin was 8.0 g/dL. Metastases to the right lung, rib cage, shoulders and a pathological fracture in the left humerus were seen on chest X-ray. The diagnosis was suspected metastatic carcinoma of the prostate (biopsy was not taken) and supportive symptomatic treatment was recommended.

The patient and his family were advised by the study staff to investigate the abnormal blood tests by the family physician, but this apparently was not done. The subject was hospitalized again on _____, due to dysphagia. A gastric tube was inserted in the emergency room. During the hospitalization the patient developed fever after an episode of aspiration. Aspiration pneumonia developed, which was treated with intravenous amikacin. The patient died on _____.

TVP-1012/233 (TEMPO Ext.) #99: This 78 year-old man received his first dose of rasagiline on _____. His medical history included "colon carcinoma with metastatic lung cancer" (diagnosed in _____ PD, carcinoma of prostate (in _____) and orthostatic hypotension. His medications were not listed in the narrative.

The participant was hospitalized on _____ due to dehydration following five days of diarrhea and fever, and was treated with intravenous fluids. Rasagiline was temporarily discontinued on _____ (study day 1498). No follow-up information is available. Although not discussed in the death narrative, descriptions in the ISS attribute his death to metastatic carcinoma of the colon.

Accidental

TVP-1012/135A (PRESTO Open Label Ext.) #555: This 70 year-old received his first dose of rasagiline on _____. His past medical history included hypercholesterolemia, angina pectoris with CABG during core study, knee replacement surgery and insomnia. Concomitant medications included levodopa/carbidopa, entacapone, aspirin, amlodipine, lovastatin, and docusates.

The participant's son informed the study investigator that the patient had died on _____ (study day 701). The patient was stated to have died from accidental

carbon monoxide poisoning while using a generator inside his home during

Complex

LARGO # 16006: This 70 year-old man received his first dose of rasagiline (1 mg/day) on . His past medical history included PD, hypertension, right bundle branch block, left anterior hemiblock and insomnia. His concomitant medications were amlodipine, clonazepam and levodopa/carbidopa.

In r he developed constipation and abdominal distension. On about abdominal x-rays revealed intestinal volvulus and megacolon. A rectal tube was placed, and the study drug was discontinued (study day 113). The participant improved and was discharged, but underwent a partial colon resection for megacolon on . On he developed fevers/rigors, and blood cultures were positive for Klebsiella. He subsequently experienced a complicated ICU course, and developed right lower lobe pneumonia. He died on of a suspected pulmonary embolism. The narrative makes no mention of the cause of death as indicated by a death certificate or autopsy.

TVP-1012/135A (PRESTO Open Label Ext.) #378: This 76 year-old woman received her first dose of rasagiline (1 mg) on . Her past medical history included hypertension, thyroid cancer with subsequent partial thyroidectomy and hypothyroidism, incontinence, arthritis, depression, right pyramidal signs, cognitive difficulties and hallucinations. Her concomitant medications were levodopa/carbidopa, pergolide, thyroxine, chlorzoxazone, paracetamol and calcium carbonate.

On the patient was hospitalized for syncope and hypotension. The investigator indicated she had periods of low blood pressure pre-dating the study, which was attributed to advanced PD. She was treated with fluids and salts. After fainting on , she was additionally treated with fludrocortisone and her pergolide was decreased.

On (868 days after study drug start) she presented to an emergency department with left-sided chest pain, and was hospitalized for a urinary tract infection. Laboratory workup was consistent with UTI and dehydration (values not given in narrative.) While hospitalized, she developed shortness of breath. On , a pulmonary workup revealed right lower lobe pneumonia. On she was discovered in cardiopulmonary arrest, resuscitated and transferred to the intensive care unit. On life sustaining measures were discontinued at the request of the family, and the patient died shortly thereafter. Death certificate or autopsy information was not given in the narrative.

Unknown

TVP-1012/233 (TEMPO Ext.) #95: This 70 year-old woman received her first dose of rasagiline (2 mg/day) on —. Her significant past medical history included PD, chronic lymphedema of the leg, and postural vertigo. She had no known history of cardiovascular disease. Her concomitant medications were not given in the narrative.

On — (study drug day 135), the participant was found dead in her apartment. The exact time of death was not known, but she had spoken to her sister the day before. The immediate cause of death listed on the death certificate was arteriosclerotic cardiovascular disease. The investigator postulated that cardiac arrest was brought about by dehydration and hot weather (temperature was stated to be ">105 degree F"). The participant was noted to have lived in an apartment without air conditioning.

During her enrollment in the study, the participant had a series of four EKGs which were reviewed by the study cardiologist. The first two were reported as showing "a possible old (or age determined [*sic*]) inferior infarct with no significant changes found during the patient's study progress." The last EKG, performed on February 23, 1999, was stated to demonstrate normal sinus rhythm, low voltage QRS, and a "small Q in AVF absent since the previous tracing."

TVP-1012/113 #1021: This 63 year-old male received his first dose of rasagiline (1 mg/day) on —. His past medical history and concomitant medications were not given in the narrative.

In — the subject was hospitalized for a paranoid disorder, and that the study drug was stopped at that time (study day 1461). During hospitalization, he developed a duodenal ulcer with acute bleeding. He was discharged from the hospital but died in his home of unknown causes five months later.

TVP-1012/233 (TEMPO Ext.) #332: This 76 year-old man received his first dose (initial dose 2 mg/day) of rasagiline on —, beginning rasagiline 1 mg/day on July 25, 2000. His past medical history was notable for PD, hypertension, peripheral vascular disease, prostate cancer and arthritis. His concomitant medications included amantadine.

On — the participant was hospitalized with diaphoresis and severe chest pressure radiating to his left arm. A Persantine Cardiolute study was reported as abnormal, and cardiac catheterization revealed triple vessel coronary artery disease with an ejection fraction of 65%. Carotid doppler study demonstrated less than 50% stenosis bilaterally. On —, the patient underwent coronary artery bypass graft surgery. During the course of the hospitalization the patient was treated with Cardizem for an episode of atrial fibrillation, which quickly converted to sinus rhythm. The patient was discharged to a skilled nursing facility on —.

On —, the participant experienced acute onset of aphasia and decreased responsiveness. He was taken to the emergency room, where he was noted to have normal vital signs and decreased movement on his right side. A brain CT showed an old

right parietal and left cerebellar infarct. MRI of the head revealed an acute left thalamic infarction and a subacute cerebellar infarction. Intracranial MRA and carotid doppler were unremarkable. EEG showed diffuse slowing with maximal slowing in the left hemisphere. While his cardiac status was considered stable, he was prescribed warfarin therapy due to the patient's intermittent history of atrial fibrillation and recent cerebral infarcts. Due to poor oral intake, a PEG tube was placed on —. The patient was discharged to a rehabilitation facility on —, at which time he was able to speak in a low voice and could walk slowly with some assistance.

The patient terminated from the study on — (study day 882), at the request of his family who were experiencing increasing difficulty transporting the patient for study visits. The study site noted the patient's death on —, after reading his obituary in the newspaper. The site was unable to obtain the cause of death.

9.3 Serious Adverse Events in Cohort 2 (Sponsor Post-Text Table 86)

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Post-Text Table 86. Cohort No. 2: Frequency and Incidence of Serious AEs by Affected Body System and COSTART Term

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)			Placebo (N=388)		
		Serious			Serious		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
-ALL	-ALL	53	30	7.9	46	31	8.0
BODY AS A WHOLE	-ALL	13	13	3.4	9	8	2.1
	ABDOMINAL PAIN	1	1	0.3	.	.	.
	ACCIDENTAL INJURY	3	3	0.8	4	3	0.8
	ASTHENIA	1	1	0.3	.	.	.
	BACK PAIN	.	.	.	1	1	0.3
	CELLULITIS	1	1	0.3	.	.	.
	CHEST PAIN	1	1	0.3	1	1	0.3
	FEVER	1	1	0.3	.	.	.
	HERNIA	1	1	0.3	1	1	0.3
	KAPOSI'S SARCOMA	1	1	0.3	.	.	.
	PAIN	1	1	0.3	.	.	.
	SEPSIS	1	1	0.3	.	.	.
	SUDDEN DEATH	.	.	.	1	1	0.3
	SUICIDE ATTEMPT	.	.	.	1	1	0.3
SURGERY & PROCEDURES	1	1	0.3	.	.	.	
CARDIOVASCULAR SYSTEM	-ALL	18	11	2.9	13	9	2.3
	AORTIC DISSECTION	.	.	.	1	1	0.3
	ARRHYTHMIA	2	2	0.5	.	.	.
	ATRIAL ARRHYTHMIA	.	.	.	1	1	0.3
	ATRIAL FIBRILLATION	.	.	.	1	1	0.3
	AV BLOCK COMPLETE	1	1	0.3	.	.	.
	AV BLOCK FIRST DEGREE	1	1	0.3	.	.	.
	AV BLOCK SECOND DEGREE	1	1	0.3	.	.	.
	BRADYCARDIA	1	1	0.3	.	.	.
	CEREBROVASCULAR ACCIDENT	2	2	0.5	1	1	0.3
	CEREBROVASCULAR DISORDER	.	.	.	1	1	0.3
	CORONARY ARTERY DISORDER	.	.	.	2	1	0.3
	HEART FAILURE	2	2	0.5	3	3	0.8
	HYPERTENSION	.	.	.	2	2	0.5
	MYOCARDIAL INFARCT	1	1	0.3	.	.	.
	MYOCARDIAL ISCHEMIA	1	1	0.3	.	.	.
	POSTURAL HYPOTENSION	2	2	0.5	.	.	.
	PULMONARY EMBOLUS	2	2	0.5	.	.	.
	SKIN VASCULITIS	.	.	.	1	1	0.3
	SYNCOPE	1	1	0.3	.	.	.
THROMBOSIS	1	1	0.3	.	.	.	
DIGESTIVE SYSTEM	-ALL	4	3	0.8	2	2	0.5
	CHOLECYSTITIS	.	.	.	1	1	0.3
	FECAL IMPACTION	1	1	0.3	.	.	.
	GASTROINTESTINAL CARCINOMA	.	.	.	1	1	0.3
	INTESTINAL OBSTRUCTION	2	2	0.5	.	.	.
	MEGACOLON	1	1	0.3	.	.	.
METABOLIC AND NUTRITIONAL DISORDERS	-ALL	1	1	0.3	1	1	0.3
	DEHYDRATION	.	.	.	1	1	0.3
	PERIPHERAL EDEMA	1	1	0.3	.	.	.
MUSCULOSKELETAL SYSTEM	-ALL	1	1	0.3	2	2	0.5
	ARTHRITIS	1	1	0.3	1	1	0.3
	MYASTHENIA	.	.	.	1	1	0.3

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)			Placebo (N=388)		
		Serious			Serious		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
NERVOUS SYSTEM	-ALL	5	5	1.3	6	6	1.5
	AKINESIA	.	.	.	1	1	0.3
	DIZZINESS	1	1	0.3	1	1	0.3
	DYSTONIA	1	1	0.3	.	.	.
	ENCEPHALOPATHY	.	.	.	1	1	0.3
	EXTRAPYRAMIDAL SYNDROME	1	1	0.3	2	2	0.5
	HALLUCINATIONS	.	.	.	1	1	0.3
	MENINGITIS	1	1	0.3	.	.	.
	SPINAL STENOSIS	1	1	0.3	.	.	.
RESPIRATORY SYSTEM	-ALL	3	3	0.8	5	5	1.3
	BRONCHITIS	1	1	0.3	.	.	.
	DYSPNEA	1	1	0.3	1	1	0.3
	LUNG EDEMA	.	.	.	1	1	0.3
	PNEUMONIA	.	.	.	3	3	0.8
	RESPIRATORY DISORDER	1	1	0.3	.	.	.
SKIN AND APPENDAGES	-ALL	3	3	0.8	3	3	0.8
	SKIN CARCINOMA	1	1	0.3	2	2	0.5
	SKIN MELANOMA	2	2	0.5	1	1	0.3
UROGENITAL SYSTEM	-ALL	5	4	1.1	5	4	1.0
	ACUTE KIDNEY FAILURE	.	.	.	1	1	0.3
	ANURIA	2	1	0.3	.	.	.
	BLADDER CARCINOMA	1	1	0.3	.	.	.
	BREAST CARCINOMA	.	.	.	1	1	0.3
	PYELONEPHRITIS	1	1	0.3	.	.	.
	URINARY RETENTION	1	1	0.3	.	.	.
	URINARY TRACT INFECTION	.	.	.	3	3	0.8

9.4 Serious Adverse Events in Cohort 9 (Sponsor Post-Text Table 93)

**APPEARS THIS WAY
ON ORIGINAL**

Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1187, Patient years=1462.9)			
		Serious			
		No. of Reports	No. of Reports Per 100 Patient Years	No. of Patients	% of Patients
-ALL	-ALL	358	24.5	183	15.4
BODY AS A WHOLE	-ALL	61	4.2	54	4.5
	ABDOMINAL PAIN	4	0.3	4	0.3
	ACCIDENTAL INJURY	14	1.0	14	1.2
	ASTHENIA	2	0.1	2	0.2
	BACK PAIN	1	0.1	1	0.1
	CELLULITIS	2	0.1	2	0.2
	CHEST PAIN	9	0.6	8	0.7
	DRUG INTERACTION	1	0.1	1	0.1
	FEVER	1	0.1	1	0.1
	FLU SYNDROME	2	0.1	1	0.1
	HEADACHE	1	0.1	1	0.1
	HERNIA	5	0.3	4	0.3
	HYDROCEPHALUS	1	0.1	1	0.1
	INFECTION	4	0.3	4	0.3
	KAPOSI'S SARCOMA	1	0.1	1	0.1
	NEOPLASM	2	0.1	1	0.1
	OVERDOSE	1	0.1	1	0.1
	PAIN	2	0.1	2	0.2
	SEPSIS	2	0.1	2	0.2
	SURGERY & PROCEDURES	6	0.4	6	0.5
CARDIOVASCULAR SYSTEM	-ALL	101	6.9	66	5.6
	ANGINA PECTORIS	16	1.1	14	1.2
	ARRHYTHMIA	2	0.1	2	0.2
	ARTERIOSCLEROSIS	2	0.1	2	0.2
	ATRIAL FIBRILLATION	10	0.7	7	0.6
	ATRIAL FLUTTER	1	0.1	1	0.1
	AV BLOCK COMPLETE	1	0.1	1	0.1
	AV BLOCK FIRST DEGREE	1	0.1	1	0.1
	AV BLOCK SECOND DEGREE	1	0.1	1	0.1
	BRADYCARDIA	1	0.1	1	0.1
	CARDIOVASCULAR DISORDER	1	0.1	1	0.1
	CEREBROVASCULAR ACCIDENT	7	0.5	7	0.6
	CORONARY ARTERY DISORDER	4	0.3	4	0.3
	CORONARY OCCLUSION	1	0.1	1	0.1
	HEART ARREST	2	0.1	2	0.2
	HEART FAILURE	4	0.3	4	0.3
	HEMORRHAGE	2	0.1	2	0.2
	HYPERTENSION	6	0.4	6	0.5
	HYPOTENSION	2	0.1	2	0.2
	MYOCARDIAL INFARCT	7	0.5	6	0.5
	MYOCARDIAL ISCHEMIA	3	0.2	3	0.3
	POSTURAL HYPOTENSION	3	0.2	3	0.3
	PULMONARY EMBOLUS	4	0.3	4	0.3
	ST ELEVATED	1	0.1	1	0.1
	SUPRAVENTRICULAR TACHYCARDIA	2	0.1	2	0.2
	SYNCOPE	8	0.5	7	0.6
	TACHYCARDIA	1	0.1	1	0.1
	THROMBOSIS	2	0.1	2	0.2
	VASCULAR DISORDER	5	0.3	4	0.3
	VENTRICULAR TACHYCARDIA	1	0.1	1	0.1

Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1187, Patient years=1462.9)				
		Serious				
		No. of Reports	No. of Reports Per 100 Patient Years	No. of Patients	% of Patients	
DIGESTIVE SYSTEM	-ALL	45	3.1	28	2.4	
	CARDIOSPASM	1	0.1	1	0.1	
	CHOLECYSTITIS	2	0.1	2	0.2	
	CHOLELITHIASIS	3	0.2	3	0.3	
	COLITIS	3	0.2	3	0.3	
	CONSTIPATION	3	0.2	3	0.3	
	DUODENAL ULCER	1	0.1	1	0.1	
	DYSPEPSIA	2	0.1	2	0.2	
	DYSPHAGIA	1	0.1	1	0.1	
	ESOPHAGEAL STENOSIS	1	0.1	1	0.1	
	ESOPHAGITIS	1	0.1	1	0.1	
	FECAL IMPACTION	1	0.1	1	0.1	
	GASTRITIS	2	0.1	2	0.2	
	GASTROINTESTINAL CARCINOMA	3	0.2	2	0.2	
	GASTROINTESTINAL DISORDER	1	0.1	1	0.1	
	GASTROINTESTINAL HEMORRHAGE	3	0.2	3	0.3	
	GI NEOPLASIA	1	0.1	1	0.1	
	INTESTINAL OBSTRUCTION	6	0.4	4	0.3	
	INTESTINAL STENOSIS	1	0.1	1	0.1	
	LARGE INTESTINE PERFORATION	1	0.1	1	0.1	
	MEGACOLON	1	0.1	1	0.1	
	MELENA	1	0.1	1	0.1	
	NAUSEA	2	0.1	2	0.2	
	STOMACH ULCER	1	0.1	1	0.1	
	STOMACH ULCER HEMORRHAGE	1	0.1	1	0.1	
	VOMITING	2	0.1	2	0.2	
	ENDOCRINE SYSTEM	-ALL	2	0.1	2	0.2
		ADH INAPPROPRIATE	2	0.1	2	0.2
	HEMIC AND LYMPHATIC SYSTEM	-ALL	5	0.3	5	0.4
		ANEMIA	2	0.1	2	0.2
HODGKIN'S LYMPHOMA		1	0.1	1	0.1	
MYELODYSPLASTIC DISORDER		1	0.1	1	0.1	
	MYELOMA	1	0.1	1	0.1	
METABOLIC AND NUTRITIONAL DISORDERS	-ALL	11	0.8	10	0.8	
	ALKALOSIS	1	0.1	1	0.1	
	DEHYDRATION	6	0.4	6	0.5	
	HYPOKALEMIA	1	0.1	1	0.1	
	HYPONATREMIA	1	0.1	1	0.1	
	PERIPHERAL EDEMA	1	0.1	1	0.1	
	WEIGHT LOSS	1	0.1	1	0.1	
MUSCULOSKELETAL SYSTEM	-ALL	16	1.1	14	1.2	
	ARTHRALGIA	3	0.2	3	0.3	
	ARTHRITIS	3	0.2	3	0.3	
	BONE DISORDER	1	0.1	1	0.1	
	JOINT DISORDER	7	0.5	7	0.6	
	OSTEOMYELITIS	1	0.1	1	0.1	
	RHABDOMYOLYSIS	1	0.1	1	0.1	

Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1187, Patient years=1462.9)				
		No. of Reports	Serious			
			No. of Reports Per 100 Patient Years	No. of Patients	% of Patients	
NERVOUS SYSTEM	-ALL	50	3.4	32	2.7	
	AGITATION	1	0.1	1	0.1	
	ANXIETY	2	0.1	2	0.2	
	CONFUSION	3	0.2	3	0.3	
	CONVULSION	3	0.2	2	0.2	
	DEMENTIA	1	0.1	1	0.1	
	DEPRESSION	6	0.4	6	0.5	
	DIZZINESS	3	0.2	3	0.3	
	DYSARTHRIA	1	0.1	1	0.1	
	DYSKINESIA	1	0.1	1	0.1	
	DYSTONIA	1	0.1	1	0.1	
	EXTRAPYRAMIDAL SYNDROME	4	0.3	3	0.3	
	HALUCINATIONS	3	0.2	3	0.3	
	HOSTILITY	1	0.1	1	0.1	
	MANIC REACTION	1	0.1	1	0.1	
	MENINGITIS	1	0.1	1	0.1	
	NEUROPATHY	4	0.3	3	0.3	
	PARESTHESIA	1	0.1	1	0.1	
	PSYCHOSIS	1	0.1	1	0.1	
	SLEEP DISORDER	1	0.1	1	0.1	
	SOMNOLENCE	1	0.1	1	0.1	
	SPINAL STENOSIS	8	0.5	8	0.7	
	TREMOR	1	0.1	1	0.1	
VERTIGO	1	0.1	1	0.1		
RESPIRATORY SYSTEM	-ALL	22	1.5	12	1.0	
	ASPIRATION PNEUMONIA	1	0.1	1	0.1	
	ASTHMA	1	0.1	1	0.1	
	BRONCHITIS	4	0.3	3	0.3	
	DYSPNEA	7	0.5	4	0.3	
	EMPHYSEMA	2	0.1	1	0.1	
	EPISTAXIS	1	0.1	1	0.1	
	LUNG DISORDER	1	0.1	1	0.1	
	PHARYNGEAL CARCINOMA	1	0.1	1	0.1	
	PNEUMONIA	3	0.2	3	0.3	
	RESPIRATORY DISORDER	1	0.1	1	0.1	
	SKIN AND APPENDAGES	-ALL	25	1.7	19	1.6
		HERPES ZOSTER	1	0.1	1	0.1
SKIN CARCINOMA		9	0.6	6	0.5	
SKIN MELANOMA		14	1.0	12	1.0	
SWEATING		1	0.1	1	0.1	
UROGENITAL SYSTEM	-ALL	20	1.4	17	1.4	
	ANURIA	2	0.1	1	0.1	
	BLADDER CARCINOMA	1	0.1	1	0.1	
	BREAST CARCINOMA	1	0.1	1	0.1	
	CYSTOCELE	1	0.1	1	0.1	
	PROSTATIC CARCINOMA	10	0.7	8	0.7	
	PROSTATIC DISORDER	2	0.1	2	0.2	
	PYELONEPHRITIS	1	0.1	1	0.1	
	URINARY RETENTION	1	0.1	1	0.1	
	VAGINAL DISORDER	1	0.1	1	0.1	

9.5 Adverse Events Associated with Early Termination in Cohort 2 (Sponsor Table 95)

Post-Text Table 95. Cohort No. 2: Frequency and Incidence of AEs Resulting in Early Termination by Affected Body System and COSTART Term

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)			Placebo (N=388)		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
-ALL	-ALL	42	16	4.2	48	19	4.9
BODY AS A WHOLE	-ALL	7	5	1.3	10	8	2.1
	ABDOMINAL PAIN	3	3	0.8	.	.	.
	ASTHENIA	1	1	0.3	4	3	0.8
	FEVER	1	1	0.3	1	1	0.3
	HEADACHE	1	1	0.3	4	4	1.0
	MALAISE	.	.	.	1	1	0.3
	PAIN	1	1	0.3	.	.	.
CARDIOVASCULAR SYSTEM	-ALL	8	5	1.3	4	3	0.8
	ARRHYTHMIA	1	1	0.3	.	.	.
	AV BLOCK COMPLETE	1	1	0.3	.	.	.
	BLOOD PRESSURE FLUCTUATIONS	1	1	0.3	.	.	.
	CEREBROVASCULAR ACCIDENT	1	1	0.3	1	1	0.3
	HEART FAILURE	1	1	0.3	1	1	0.3
	HYPERTENSION	.	.	.	2	2	0.5
	POSTURAL HYPOTENSION	2	2	0.5	.	.	.
	SYNCOPE	1	1	0.3	.	.	.
	.	.	.	.	.	.	.
DIGESTIVE SYSTEM	-ALL	5	4	1.1	9	6	1.5
	CONSTIPATION	1	1	0.3	.	.	.
	DRY MOUTH	.	.	.	1	1	0.3
	DYSPEPSIA	1	1	0.3	.	.	.
	FLATULENCE	.	.	.	1	1	0.3
	GASTROINTESTINAL HEMORRHAGE	1	1	0.3	.	.	.
	NAUSEA	1	1	0.3	6	6	1.5
	VOMITING	1	1	0.3	1	1	0.3
	.	.	.	.	.	.	.
HEMIC AND LYMPHATIC SYSTEM	-ALL	1	1	0.3	.	.	.
	ANEMIA	1	1	0.3	.	.	.
METABOLIC AND NUTRITIONAL DISORDERS	-ALL	1	1	0.3	2	2	0.5
	PERIPHERAL EDEMA	1	1	0.3	1	1	0.3
	WEIGHT LOSS	.	.	.	1	1	0.3
MUSCULOSKELETAL SYSTEM	-ALL	.	.	.	1	1	0.3
	MYASTHENIA	.	.	.	1	1	0.3
NERVOUS SYSTEM	-ALL	12	7	1.8	16	12	3.1
	DIZZINESS	2	2	0.5	4	3	0.8
	DYSKINESIA	1	1	0.3	3	3	0.8
	ENCEPHALOPATHY	.	.	.	1	1	0.3
	EXTRAPYRAMIDAL SYNDROME	.	.	.	4	4	1.0
	HALLUCINATIONS	2	2	0.5	1	1	0.3
	HYPERKINESIA	1	1	0.3	.	.	.
	MENINGITIS	1	1	0.3	.	.	.
	NYSTAGMUS	1	1	0.3	.	.	.
	PARESTHESIA	1	1	0.3	1	1	0.3
	PERSONALITY DISORDER	1	1	0.3	.	.	.
	SOMNOLENCE	1	1	0.3	1	1	0.3
	VERTIGO	1	1	0.3	1	1	0.3
	.	.	.	.	.	.	.
	RESPIRATORY SYSTEM	-ALL	2	2	0.5	1	1
DYSPNEA		2	2	0.5	1	1	0.3
SKIN AND APPENDAGES	-ALL	1	1	0.3	1	1	0.3
	RASH	1	1	0.3	.	.	.
	URTICARIA	.	.	.	1	1	0.3
SPECIAL SENSES	-ALL	1	1	0.3	2	2	0.5
	ABNORMAL VISION	.	.	.	1	1	0.3
	EYE DISORDER	1	1	0.3	.	.	.
	EYE PAIN	.	.	.	1	1	0.3

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)			Placebo (N=388)		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
UROGENITAL SYSTEM	-ALL	4	2	0.5	2	1	0.3
	ACUTE KIDNEY FAILURE	-	-	-	1	1	0.3
	ANURIA	2	1	0.3	-	-	-
	DYSURIA	1	1	0.3	-	-	-
	URINARY TRACT INFECTION	1	1	0.3	1	1	0.3

*AEs with Action Taken with study Drug: Dose Stopped and Termination Reason : "Due to AE"

9.6 Adverse Events associated with Early Termination for all Participants Exposed to Rasagiline (120 Day Update Post-Text Table 47)

120 Day Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1360)		
		No. of Reports	No. of Patients	% of Patients
-ALL	-ALL	262	128	9.4
BODY AS A WHOLE	-ALL	40	35	2.6
	ABDOMINAL PAIN	6	6	0.4
	ACCIDENTAL INJURY	7	7	0.5
	ASTHENIA	5	4	0.3
	BACK PAIN	1	1	0.1
	CHEST PAIN	3	3	0.2
	FEVER	4	4	0.3
	FLU SYNDROME	1	1	0.1
	HEADACHE	5	5	0.4
	HEMOTHORAX	1	1	0.1
	INFECTION	2	2	0.1
	LAB TEST ABNORMAL	1	1	0.1
	MALAISE	1	1	0.1
	OVERDOSE	1	1	0.1
	PAIN	1	1	0.1
PERITONITIS	1	1	0.1	
CARDIOVASCULAR SYSTEM	-ALL	45	37	2.7
	ARRHYTHMIA	1	1	0.1
	ARTERIOSCLEROSIS	1	1	0.1
	ATRIAL FIBRILLATION	2	2	0.1
	AV BLOCK COMPLETE	1	1	0.1
	BLOOD PRESSURE FLUCTUATIONS	2	2	0.1
	BUNDLE BRANCH BLOCK	1	1	0.1
	CEREBROVASCULAR ACCIDENT	3	3	0.2
	DEEP THROMBOPHLEBITIS	1	1	0.1
	ELECTROCARDIOGRAM ABNORMAL	2	2	0.1
	HEART FAILURE	1	1	0.1
	HYPERTENSION	9	9	0.7
	HYPOTENSION	1	1	0.1
	MYOCARDIAL INFARCT	1	1	0.1
	MYOCARDIAL ISCHEMIA	1	1	0.1
	PALPITATION	1	1	0.1
	PERIPHERAL VASCULAR DISORDER	1	1	0.1
	POSTURAL HYPOTENSION	7	7	0.5
	SKIN VASCULITIS	1	1	0.1
	SYNCOPE	5	5	0.4
	TACHYCARDIA	2	2	0.1
	VENTRICULAR TACHYCARDIA	1	1	0.1

120 Day Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1360)		
		No. of Reports	No. of Patients	% of Patients
DIGESTIVE SYSTEM	-ALL	43	28	2.1
	ANOREXIA	1	1	0.1
	CONSTIPATION	2	2	0.1
	DIARRHEA	2	2	0.1
	DYSPEPSIA	2	2	0.1
	DYSPHAGIA	1	1	0.1
	GASTROINTESTINAL CARCINOMA	4	3	0.2
	GASTROINTESTINAL DISORDER	1	1	0.1
	GASTROINTESTINAL HEMORRHAGE	2	2	0.1
	INTESTINAL OBSTRUCTION	1	1	0.1
	INTESTINAL PERFORATION	1	1	0.1
	INTESTINAL STENOSIS	1	1	0.1
	LIVER FUNCTION TESTS ABNORMAL	11	4	0.3
	NAUSEA	9	9	0.7
	STOMACH ULCER HEMORRHAGE	1	1	0.1
	VOMITING	4	4	0.3
ENDOCRINE SYSTEM	-ALL	2	2	0.1
	ADH INAPPROPRIATE	1	1	0.1
	HYPERTHYROIDISM	1	1	0.1
HEMIC AND LYMPHATIC SYSTEM	-ALL	6	4	0.3
	ANEMIA	5	3	0.2
	MYELOMA	1	1	0.1
METABOLIC AND NUTRITIONAL DISORDERS	-ALL	7	7	0.5
	BILIRUBINEMIA	1	1	0.1
	DEHYDRATION	1	1	0.1
	HYPERTHYROIDISM	1	1	0.1
	HYPONATREMIA	1	1	0.1
	PERIPHERAL EDEMA	1	1	0.1
	WEIGHT LOSS	2	2	0.1
MUSCULOSKELETAL SYSTEM	-ALL	2	1	0.1
	ARTHRALGIA	2	1	0.1

120 Day Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1360)		
		No. of Reports	No. of Patients	% of Patients
NERVOUS SYSTEM	-ALL	82	53	3.9
	ABNORMAL GAIT	1	1	0.1
	AGITATION	2	2	0.1
	ANXIETY	2	2	0.1
	ATAXIA	1	1	0.1
	CIRCUMORAL PARESTHESIA	1	1	0.1
	CONVULSION	1	1	0.1
	DEPRESSION	6	6	0.4
	DIZZINESS	8	8	0.6
	DYSKINESIA	5	5	0.4
	EXTRAPYRAMIDAL SYNDROME	4	4	0.3
	HALLUCINATIONS	16	14	1.0
	HEMIPLEGIA	1	1	0.1
	HOSTILITY	1	1	0.1
	HYPERKINESIA	1	1	0.1
	HYPERTONIA	1	1	0.1
	MANIC DEPRESSIVE REACTION	1	1	0.1
	MANIC REACTION	1	1	0.1
	MENINGITIS	1	1	0.1
	NEUROPATHY	1	1	0.1
	NYSTAGMUS	1	1	0.1
	PARANOID REACTION	1	1	0.1
	PARESTHESIA	7	4	0.3
	PERSONALITY DISORDER	1	1	0.1
	PSYCHOSIS	5	4	0.3
	SLEEP DISORDER	3	3	0.2
	SOMNOLENCE	1	1	0.1
THINKING ABNORMAL	2	2	0.1	
TREMOR	2	2	0.1	
VERTIGO	4	3	0.2	
RESPIRATORY SYSTEM	-ALL	10	6	0.4
	ASPIRATION PNEUMONIA	1	1	0.1
	ASTHMA	1	1	0.1
	BRONCHITIS	1	1	0.1
	DYSPNEA	4	3	0.2
	PNEUMONIA	2	2	0.1
	RESPIRATORY DISORDER	1	1	0.1
SKIN AND APPENDAGES	-ALL	17	13	1.0
	DRY SKIN	1	1	0.1
	PRURITUS	2	2	0.1
	RASH	4	4	0.3
	SKIN MELANOMA	8	6	0.4
	SWEATING	1	1	0.1
	URTICARIA	1	1	0.1
SPECIAL SENSES	-ALL	2	2	0.1
	EYE DISORDER	1	1	0.1
	RETINAL DISORDER	1	1	0.1
UROGENITAL SYSTEM	-ALL	6	4	0.3
	ANURIA	2	1	0.1
	BREAST CARCINOMA	1	1	0.1
	DYSURIA	1	1	0.1
	URINARY TRACT INFECTION	2	2	0.1

* AEs with Action Taken: Dose Stopped and Termination Reason : Due to AE

9.7 Laboratory Normal and Potentially Clinically Significant Limits (Sponsor Table 2- PRESTO Study Report. A similar table is also provided as Table 2 within the LARGO Study Report)

Test name	Unit	Gender	Age (years)	Lower Normal Range	Upper Normal Range	Lower Clinically Significant Range	Upper Clinically Significant Range
WBC	x10 ³ /cumm	Both	All	4.8	10.8	2.8	16
Neutrophils	%	Both	All	43	75	.	.
Lymphocytes	%	Both	All	21	51	.	.
Monocytes	%	Both	All	4	15	.	.
Eosinophils	%	Both	All	0	6	.	.
Basophils	%	Both	All	0	2	.	.
Neutrophils absolute	x10 ³ /uL	Both	All	1.8	7.8	1.5	10
Lymphocytes absolute	x10 ³ /uL	Both	All	1	4.8	.	.
Monocytes absolute	x10 ³ /uL	Both	All	0	0.8	.	.
Eosinophils absolute	x10 ³ /uL	Both	All	0	0.45	.	.
Basophils absolute	x10 ³ /uL	Both	All	0	0.2	.	.
RBC	x10 ⁶ /cumm	Female	39-83	4.2	5.4	.	.
RBC	x10 ⁶ /cumm	Male	32-84	4.6	6.2	.	.
Hgb	gm/dL	Female	39-83	12	16	10	.
Hgb	gm/dL	Male	32-84	13.5	18	11.5	.
Hct	%	Female	39-83	38	47	.	.
Hct	%	Male	32-84	40	54	.	.
MCV	fL	Both	All	81	99	.	.
MCH	PG	Both	All	28	32	.	.
MCHC	%	Both	All	32	36	.	.
Platelets count	x10 ³ /cumm	Both	All	130	400	75	700
Sodium	mmol/L	Both	All	135	148	130	150
Potassium	mmol/L	Both	All	3.5	5.3	2.5	5.5
Chloride	mmol/L	Both	All	98	109	.	.
Glucose	mg/dL	Both	All	60	110	50	250
Creatinine	mg/dL	Both	All	0.4	1.5	.	2
Calcium	mg/dL	Both	All	8.4	10.4	7.5	12
Phosphorus	mg/dL	Both	All	2.5	4.8	1.5	6
Bilirubin, total	mg/dL	Both	All	0.3	1.5	.	2
Alkaline phosphatase	U/L	Both	All	37	147	.	441
GGTP	U/L	Both	All	1	50	.	150
AST (SGOT)	U/L	Both	All	5	45	.	135
ALT (SGPT)	U/L	Both	All	1	55	.	165
Protein, total	g/dL	Both	All	6	8	4	10
Albumin	g/dL	Both	All	3.5	5	2.5	.
Cholesterol	mg/dL	Both	All	120	199	.	.
LDH	U/L	Both	All	103	223	.	669
BUN	mg/dL	Both	All	6	22	.	40
pH		Both	All	5.5	7	.	.
Urine WBCs	/HPF	Both	All	0	5	.	.
Urine RBCs	/HPF	Both	All	0	5	.	.
Specific gravity		Both	All	1.01	1.03	.	.

9.8 Number and Percent of Subjects with Shifts from Low/Normal to High and High/Normal to Low from Cohort 1 Biochemistry Results (Sponsor Post-Text Table 101)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment	Rasagiline 1 mg (N=149)									Rasagiline 2 mg (N=146)									Placebo (N=151)								
	All	Change From High / Normal to Low			Change From Low / Normal to High			Other (%)	All	Change From High / Normal to Low			Change From Low / Normal to High			Other (%)	All	Change From High / Normal to Low			Change From Low / Normal to High			Other (%)			
		N	N	%	N	%	N			%	N	%	N	%	N			%	N	%	N	%	N		%	N	%
	Electrolytes	SODIUM (mEq/L)	148	3	2.0	1	0.7	144	97.3	148	2	1.4	1	0.7	142	97.9	151	2	1.3	4	2.6	145	96.0				
POTASSIUM (mEq/L)		148	1	0.7	1	0.7	146	98.6	145					145	100.0	150	1	0.7			149	99.3					
CHLORIDE (mEq/L)		148	1	0.7			147	99.3	148					148	100.0	151					151	100.0					
Liver Function	BILIRUBIN (TOTAL) (mg/dL)	148			2	1.4	146	98.6	145					3	2.1	142	97.9	151			4	2.6	147	97.4			
	ALKALINE PHOSPHATASE (U/L)	148	1	0.7	3	2.0	144	97.3	145					145	100.0	151	2	1.3	2	1.3	147	97.3					
	SGOT (AST) (U/L)	148	1	0.7	4	2.7	143	96.6	145					145	100.0	151	1	0.7	5	3.3	145	96.0					
	SGPT (ALT) (U/L)	148			5	3.4	143	96.6	145					2	1.4	143	98.6	151			4	2.6	147	97.4			
	GGT (U/L)	133			2	1.5	131	98.5	131					4	3.1	127	96.9	138	1	0.7	5	3.6	132	98.7			
Renal Function	CREATININE (mg/dL)	148			6	4.1	142	95.9	145					1	0.7	144	99.3	151			3	2.0	148	98.0			
	UREA NITROGEN (BUN) (mg/dL)	148			6	4.1	142	95.9	145					5	3.4	140	96.6	151			1	0.7	150	99.3			
Other Parameters	CALCIUM (mg/dL)	148	1	0.7	1	0.7	146	98.6	145	2	1.4			143	98.6	151	1	0.7			150	99.3					
	PHOSPHORUS (mg/dL)	148	1	0.7			147	99.3	145	1	0.7			144	99.3	150	1	0.7			149	99.3					
	GLUCOSE (mg/dL)	148	1	0.7	15	10.1	132	89.2	145	7	4.8	14	9.7	124	85.5	150	4	2.7	7	4.7	139	92.7					
	CHOLESTEROL (mg/dL)	148	13	8.8	3	2.0	132	89.2	145	12	8.3			133	91.7	151	13	8.6	1	0.7	137	90.7					
	PROTEIN (TOTAL) (g/dL)	148			1	0.7	147	99.3	145	2	1.4			143	98.6	151					151	100.0					
	ALBUMIN (g/dL)	148	2	1.4			146	98.6	145	1	0.7			144	99.3	151					151	100.0					
	LDH (U/L)	148					148	100.0	145					1	0.7	144	99.3	150			1	0.7	149	99.3			

*Other: Stayed in the same condition or moved to "Within Normal"

9.9 Number and Percent of Subjects with Shifts from Low/Normal to High and High/Normal to Low from Cohort 2 Biochemistry Results (Sponsor Post-Text Table 102)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	Rasagiline 1 mg (N=380)									Placebo (N=388)								
	All	Change From High / Normal to Low			Change From Low / Normal to High			Other (%)	All	Change From High / Normal to Low			Change From Low / Normal to High			Other (%)		
		N	N	%	N	%	N			%	N	%	N	%	N		%	
	Electrolytes	SODIUM (mEq/L)	378	2	0.5	1	0.3	377	99.2	384	1	0.3			383	99.7		
POTASSIUM (mEq/L)		378			5	1.3	370	98.7	384	2	0.5	2	0.5	380	99.0			
CHLORIDE (mEq/L)		378	4	1.1	13	3.7	367	95.2	384	1	0.3	22	5.7	361	94.0			
Liver Function	BILIRUBIN (TOTAL) (mg/dL)	378	2	0.5	6	1.6	367	97.9	384	5	1.3	5	1.3	374	97.4			
	ALKALINE PHOSPHATASE (U/L)	378			9	2.4	366	97.6	384	1	0.3	7	1.8	376	97.9			
	SGOT (AST) (U/L)	378			1	0.3	374	99.7	384			3	0.8	381	99.2			
	SGPT (ALT) (U/L)	378			2	0.5	373	99.5	384			3	0.8	381	99.2			
	GGT (U/L)	378			4	1.1	371	98.9	384			5	1.3	379	98.7			
Renal Function	CREATININE (mg/dL)	378	3	0.8			372	99.2	384	5	1.3	3	0.8	376	97.9			
	UREA NITROGEN (BUN) (mg/dL)	378			25	6.7	350	93.3	384			21	5.5	363	94.5			
Other Parameters	CALCIUM (mg/dL)	378			11	2.9	364	97.1	384	3	0.8	3	0.8	378	98.4			
	PHOSPHORUS (mg/dL)	378	3	0.8	6	1.6	366	97.6	384	7	1.8	2	0.5	375	97.7			
	GLUCOSE (mg/dL)	378	3	0.8	22	5.9	350	93.3	384	3	0.8	27	7.0	354	92.2			
	CHOLESTEROL (mg/dL)	378	2	0.5	28	7.5	345	92.0	384	1	0.3	31	8.1	352	91.7			
	PROTEIN (TOTAL) (g/dL)	378	3	0.8	8	2.1	367	97.9	384	2	0.5			382	99.5			
	ALBUMIN (g/dL)	378	2	0.5			373	99.5	384	2	0.5			382	99.5			
	LDH (U/L)	378	1	0.3	9	2.4	365	97.3	384	1	0.3	14	3.6	369	96.1			

*Other: Stayed in the same condition or moved to "Within Normal"

9.10 Narratives for Selected Cohort 2 Participants with PCS Biochemistry Lab Changes

TEMPO #45: This 71-year-old woman was randomized on to rasagiline 1mg/day, and experienced low serum glucose on Week 26. The subject's concomitant medication did not include an oral hypoglycemic: hydrochlorothiazide, triamterene, propranolol, methylprednisolone, famotidine, potassium, estrogen supplement, medroxyprogesterone, mirtazapine and guaiphenesin (TEMPO Datafile CMED).

Glucose values before and after week 26

17 Feb. 98 100
 23 Feb. 98 94 Baseline
 01 Jun. 98 101

24 Aug. 98 44 Week 26
 05 Oct. 98 58
 24 Feb. 99 92

TEMPO #123: This 68 year-old woman receiving rasagiline 1 mg/day experienced a single borderline-low serum sodium (129 MEQ/L) at Week 14 of the study.

TEMPO #288: This 69 year-old man receiving rasagiline 1 mg/day was found to have an isolated elevated GGT (170 U/L) at Week 14.

TEMPO #319: This 68 year-old woman receiving rasagiline 12 mg/day experienced a single borderline low serum sodium (128 MEQ/L) at her Week 14 visit.

TEMPO #335: This 72 year-old woman receiving rasagiline 1 mg/day experienced persistent elevated GGT from study screening through the conclusion of the study.

GGT Value	Study Week
342	Screening
369	Baseline
206	Retest
226	Week 14
469	Termination

9.11 Narratives for Selected Cohort 2 Participants with PCS Biochemistry Lab Changes

TVP-1012/231 #205: This 53 year-old man receiving rasagiline 1 mg/day experienced the following PCS laboratory results: Week 26: Total Bilirubin 1.3 mg/dL, Alkaline phosphatase 116 U/L, Glucose 124 /dL Week 27: Alkaline phosphatase: 114 U/L

TVP-1012/231 #703: This 51 year-old man experienced the following PCS laboratory results throughout the study:

Date	Test	Result
Baseline	BILIRUBIN (TOTAL) (mg/dL)	1.2
04APR1996	BILIRUBIN (TOTAL) (mg/dL)	1.7
	GLUCOSE (mg/dL)	139.0
	ALT (SGPT)	25
22APR1996	BILIRUBIN (TOTAL) (mg/dL)	1.7
	ALT (SGPT)	24
06MAY1996	GLUCOSE (mg/dL)	119.0
	BILIRUBIN (TOTAL) (mg/dL)	2.3
	ALT (SGPT)	33
20MAY1996	GLUCOSE (mg/dL)	126.0
	BILIRUBIN (TOTAL) (mg/dL)	2.1
	ALT (SGPT)	21
06JUN1996	BILIRUBIN (TOTAL) (mg/dL)	1.6
	ALT (SGPT)	25
13JUN1996	BILIRUBIN (TOTAL) (mg/dL)	2.3
	ALT (SGPT)	33
27JUN1996	BILIRUBIN (TOTAL) (mg/dL)	2.5
	ALT (SGPT)	33
23JUL1996	BILIRUBIN (TOTAL) (mg/dL)	2.6
	ALT (SGPT)	25
14AUG1996	BILIRUBIN (TOTAL) (mg/dL)	1.4

TEMPO #335: This 72 year-old woman, receiving rasagiline 1 mg, experienced elevated liver function tests at baseline and throughout the study. The sponsor reports the subject had a 15 year history of intermittent abnormal liver function tests.

SGOT (U/L) values throughout the study

22 Dec. 97	187	Baseline
22 June 98	133	Week 26
3 Aug. 98	147	Week 32
22 Dec. 98	206	Week 52
4 Feb. 99	83	Week 58 (after six weeks washout)

SGPT (U/L) values throughout the study

22 Dec. 97	145	Baseline
22 June 98	82	Week 26
3 Aug. 98	92	Week 32
22 Dec. 98	93	Week 52
4 Feb. 99	52	Week 58 (after six weeks washout)

GGT (U/L) values throughout the study

22 Dec. 97	369	Baseline
22 June 98	469	Week 26
3 Aug. 98	511	Week 32
22 Dec. 98	1072	Week 52
4 Feb. 99	550	Week 58 (after six weeks washout)

LDH (U/L) values throughout the study

22 Dec. 97	320	Baseline
22 June 98	284	Week 26
3 Aug. 98	296	Week 32
22 Dec. 98	328	Week 52
4 Feb. 99	311	Week 58 (after six weeks washout)

9.12 Number and Frequency of Shifts from Low/Normal to High and High/Normal to Low from Cohort 1 Hematology Results (Sponsor Table 63)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment	Rasagiline 1 mg (N=149)									Rasagiline 2 mg (N=146)									Placebo (N=151)								
	Change From High /Normal to Low			Change From Low /Normal to High			Other (*)			Change From High /Normal to Low			Change From Low /Normal to High			Other (*)			Change From High /Normal to Low			Change From Low /Normal to High			Other (*)		
	All	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
WHITE BLOOD CELLS (x10 ³ /uL)	148	7	4.7	1	0.7	140	94.6	148	4	2.8	2	1.4	139	95.9	151	4	2.6	1	0.7	146	96.7						
RED BLOOD CELLS (x10 ⁶ /uL)	148	6	4.1			142	95.9	145	6	4.1			139	95.9	151	6	4.0	1	0.7	144	95.4						
HEMOGLOBIN (g/dL)	148	4	2.7			144	97.3	145	2	1.4			143	98.6	151	2	1.3	1	0.7	148	98.0						
HEMATOCRIT (%)	148	5	3.4			143	96.6	145	4	2.8			141	97.2	151	2	1.3	1	0.7	148	98.0						
NEUTROPHILS (x10 ³ /uL)	133	9	6.8			124	93.2	131	2	1.5	1	0.8	129	97.7	138	2	1.4	1	0.7	135	97.8						
NEUTROPHILS (%)	133	1	0.8	3	2.3	129	97.0	131			6	4.6	125	95.4	138	2	1.4	3	2.2	133	96.4						
LYMPHOCYTES (%)	133	2	1.5	2	1.5	129	97.0	131	3	2.3			128	97.7	138	2	1.4	1	0.7	135	97.8						
LYMPHOCYTES (x10 ³ /uL)	133	3	3.0	2	1.5	127	95.5	131	5	3.8	1	0.8	125	95.4	138	3	2.2	2	1.4	133	96.4						
MONOCYTES (%)	133	2	1.5	10	7.5	121	91.0	131			2	1.5	129	98.5	138	1	0.7	4	2.9	133	96.4						
MONOCYTES (x10 ³ /uL)	133					133	100.0	131					131	100.0	138	2	1.4			136	98.6						
EOSINOPHILS (%)	133			3	2.3	130	97.7	131			2	1.5	129	98.5	138			3	2.2	135	97.8						
EOSINOPHILS (x10 ³ /uL)	133			1	0.8	132	99.2	131					131	100.0	138					138	100.0						
BASOPHILS (%)	133					133	100.0	131					131	100.0	138			2	1.4	136	98.6						
BASOPHILS (x10 ³ /uL)	133					133	100.0	131					131	100.0	138					138	100.0						
PLATELETS (x10 ³ /uL)	147			1	0.7	146	99.3	145	2	1.4			143	98.6	151			1	0.7	150	99.3						
MCV (fL)	133			4	3.0	129	97.0	131			1	0.8	130	99.2	138	1	0.7	2	1.4	135	97.8						

*Other: Stayed in the same condition or moved to "Within Normal"

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9.13 Narratives of Selected Cohort 1 Participants with Hematological PCS Results

TEMPO #91: This 58-year-old man randomized to rasagiline (1 mg/day) experienced below-range hemoglobin level at Week 26 (June 1998). The sponsor states that the patient suffered from

a urinary tract infection from _____, and notes that the hemoglobin level returned to baseline after the single abnormal measurement.

Hemoglobin values before and after week 26

Visit Date	Hemoglobin (g/dL)
08 Dec. 97	15.0
16 Dec. 97	14.6 Baseline
30 Mar. 98	14.3
19 Jun. 98	11.0 Week 26
31 Jul. 98	14.1
11 Dec. 98	15.1
28 Jan. 99	15.0

TEMPO #279: This 66-year-old Black female was randomized to rasagiline 2 mg/day. The sponsor notes she had a below-range leukocyte count starting from the baseline through Week 26, which was attributed to benign ethnic neutropenia.

WBC values before and after week 26

05 Aug. 98	3.02
26 Aug. 98	2.98 Baseline
03 Dec. 98	2.62
24 Feb. 99	2.56 Week 26
07 Apr. 99	2.49
25 Aug. 99	2.58

TEMPO #300: This 49-year-old man was randomized on to rasagiline 1 mg/day. Teva notes that a below-range leukocyte count was observed at the baseline visit, prior to exposure to the study drug. Leukocyte levels returned to normal during treatment, four weeks later.

WBC values before and after baseline

08 Jan. 98	5.13 Screening
08 Feb. 98	2.92 Baseline
	4.95
	4.33
07 Jul. 99	4.09 Week 26

TEMPO #186: This 44-year-old man was randomized to rasagiline 1mg/day. The sponsor notes that the subject presented with a marginally low leukocyte count at baseline, which was lower four weeks later, at the end of the double-blind, placebo-controlled phase of the study. The patient terminated this phase of the study early - at Week 4 - and started the active-treatment phase, due to a need for additional dopaminergic therapy. His leukocyte count returned to normal eight weeks later, on active-treatment, and declined again at the end of the active-treatment phase of the study. Six weeks after discontinuing treatment with the study drug (week 58) the patient's leukocyte count remained below range. Teva notes that fluctuations in laboratory results occurred prior to exposure to the study drug (from screening to baseline during a six-day interval) and on active-treatment.

BC values before and after baseline

12 Aug. 98	5.59 Screening
18 Aug. 98	3.61 Baseline
17 Sept. 98	2.91 Week 26 = week 4
28 Oct. 98	5.07 Week 32
31 Mar 99	2.91 Week 52
07 May 99	2.71 Week 58 after 6 weeks washout

TEMPO #427: This 74-year-old man began receiving rasagiline (1 mg/day) on December 18, 1998. He had a below-range leukocyte count at approximately Week 26 (April and June 1999). The sponsor notes that normal leukocyte counts were recorded both before and after the two decreased measurements.

WBC values before and after week 26

01 Dec. 98 4.99
 18 Dec. 98 4.17 Baseline
 09 Apr. 99 **2.95**
 25 Jun. 99 **2.77** Week 26
 03 Aug. 99 4.96
 14 Dec. 99 3.54

9.14 Number and Frequency of Shifts from Low/Normal to High and High/Normal to Low for Cohort 2 Hematology Results (Sponsor Post-Text Table 65)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	Rasagiline 1 mg (N=380)								Placebo (N=388)							
	All		Change From High /Normal to Low		Change From Low /Normal to High		Other (*)		All		Change From High /Normal to Low		Change From Low /Normal to High		Other (*)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
WHITE BLOOD CELLS (x10 ³ /uL)	373	13	3.5	4	1.1	356	95.4	384	12	3.1	7	1.8	365	95.1		
RED BLOOD CELLS (x10 ⁶ /uL)	373	25	6.7	2	0.5	346	92.8	384	20	5.2	.	.	364	94.8		
HEMOGLOBIN (g/dL)	373	25	6.7	1	0.3	347	93.0	384	16	4.2	.	.	368	95.8		
HEMATOCRIT (%)	373	28	7.5	3	0.8	342	91.7	384	16	4.2	4	1.0	364	94.8		
NEUTROPHILS (x10 ³ /uL)	373	2	0.5	7	1.9	364	97.6	384	.	.	6	1.6	378	98.4		
NEUTROPHILS (%)	373	.	.	27	7.2	346	92.8	384	.	.	29	7.6	355	92.4		
LYMPHOCYTES (x10 ³ /uL)	373	7	1.9	.	.	366	98.1	384	19	4.9	1	0.3	364	94.8		
LYMPHOCYTES (%)	373	27	7.2	2	0.5	344	92.2	384	33	8.6	3	0.8	348	90.6		
MONOCYTES (x10 ³ /uL)	373	17	4.6	1	0.3	355	95.2	384	26	6.8	3	0.8	355	92.4		
MONOCYTES (%)	373	13	3.5	1	0.3	359	96.2	384	17	4.4	.	.	367	95.6		
EOSINOPHILS (x10 ³ /uL)	373	10	2.7	5	1.3	358	96.0	384	15	3.9	5	1.3	364	94.8		
EOSINOPHILS (%)	373	.	.	9	2.4	364	97.6	384	.	.	7	1.8	377	98.2		
BASOPHILS (%)	373	.	.	1	0.3	372	99.7	384	.	.	.	.	384	100.0		
BASOPHILS (x10 ³ /uL)	373	.	.	.	.	373	100.0	384	.	.	.	.	384	100.0		
PLATELETS (x10 ³ /uL)	372	5	1.3	3	0.8	364	97.8	383	4	1.0	2	0.5	377	98.4		
MCH (pg)	373	3	0.8	10	2.7	360	96.5	384	1	0.3	11	2.9	372	96.9		
MCHC (%)	373	22	5.9	.	.	351	94.1	384	35	9.1	.	.	349	90.9		
MCV (fL)	373	3	0.8	11	2.9	359	96.2	384	1	0.3	16	4.2	367	95.6		

*Other=Stayed in the same condition or moved to "Within Normal"

9.15 Shift Analysis for Urinalysis from Baseline to LOV for TEMPO, LARGO and PRESTO

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Post-Text Table 103. Study TEMPO Placebo-Controlled Phase: Shift Analysis from Baseline to Last Observed Value (LOV) for Urinalysis Results

Protocol: TEMPO Placebo-Controlled Phase	1 MG								2 MG								PLACEBO							
	Change From Abnormal to Normal			Change From Normal to Abnormal			No Change		Change From Abnormal to Normal			Change From Normal to Abnormal			No Change		Change From Abnormal to Normal			Change From Normal to Abnormal			No Change	
	All	N	%	N	%	N	%	All	N	%	N	%	N	%	All	N	%	N	%	N	%	N	%	
Parameter	131					131	100.0	129					129	100.0	138					138	100.0			
URINE CASTS	131					131	100.0	129					129	97.7	138					138	100.0			
URINE GLUCOSE	131	1	0.8			130	99.2	129	1	0.8			128	99.2	138	1	0.7			137	99.3			
URINE KETONS	131	2	1.5	8	6.1	121	92.4	129	5	3.9	4	3.1	120	93.0	138	5	3.6	10	7.2	123	89.1			
URINE OCCULT BLOOD	131					131	100.0	129					129	100.0	138					138	100.0			
URINE PH	131	2	1.5		0.8	128	97.7	129	1	0.8	3	2.3	125	96.0	138	2	1.4	1	0.7	135	97.8			
URINE PROTEIN	131	3	2.3	2	1.5	126	96.2	129	4	3.1	3	2.3	122	94.6	138	7	5.1	5	3.6	126	91.3			
URINE RBC	131	1	0.8	5	3.8	125	95.4	129	1	0.8	2	1.6	126	97.7	138	2	1.4	6	4.3	130	94.2			
URINE WBC	131					131	100.0	129					129	100.0	138					138	100.0			

Post-Text Table 104. Study LARGO: Shift Analysis from Baseline to Last Observed Value (LOV) for Urinalysis Results

LARGO (LARGO)	Rasagiline 1 mg								Placebo										
	All		Change From Abnormal to Normal		Change From Normal to Abnormal		Other*		All		Change From Abnormal to Normal		Change From Low /Normal to High		Change From Normal to Abnormal		Other*		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
pH	228						228	100.0	225					1	0.44			224	99.56
PROTEIN	228	23	10.09	12	5.26	193	84.65	225	16	7.11				15	6.67	194	86.22		
GLUCOSE	228	3	1.32	1	0.44	224	98.25	225	2	0.89				2	0.89	221	98.22		
KETONES	228	30	13.16	21	9.21	177	77.63	225	29	12.89				29	12.89	167	74.22		
WBC (HPF)	228	20	8.77	23	10.09	185	81.14	225	16	7.11				28	12.44	181	80.44		
RBC (HPF)	228	11	4.82	10	4.39	207	90.79	225	12	5.33				10	4.44	203	90.22		

*Other: Stayed at the Same Condition or Moved to Within Normal

1 mg

PRESTO (PRESTO)	All	Change From Abnormal to Normal		Change From High /Normal to Low		Change From Low /Normal to High		Change From Normal to Abnormal		Other*	
		N	%	N	%	N	%	N	%	N	%
pH	143			16	11.19	6	4.20			121	84.62
PROTEIN	143	7	4.90					7	4.90	129	90.21
URINE GLUCOSE	143	2	1.40							141	98.60
KETONES	143	16	11.19					23	16.08	104	72.73
URINE WBCS (HPF)	143	8	5.59					8	5.59	127	88.81
URINE RBCS (HPF)	143	1	0.70					1	0.70	141	98.60
OCCULT BLOOD	143	3	2.10					1	0.70	139	97.20

Placebo

PRESTO (PRESTO)	All	Change From Abnormal to Normal		Change From High /Normal to Low		Change From Low /Normal to High		Change From Normal to Abnormal		Other*	
		N	%	N	%	N	%	N	%	N	%
pH	158			11	6.96	7	4.43			140	88.61
PROTEIN	158	3	1.90					9	5.70	146	92.41
URINE GLUCOSE	158	1	0.63					1	0.63	156	98.73
KETONES	158	20	12.66					14	8.86	124	78.48
URINE WBCS (HPF)	158	11	6.96					14	8.86	133	84.18
URINE RBCS (HPF)	158	3	1.90					3	1.90	152	96.20
OCCULT BLOOD	158	1	0.63					3	1.90	154	97.47

9.16 Number and Percent of Cohort 2 Subjects Reporting AEs by Dopamine Agonist Use (Sponsor ISS Table 56)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	LARGO and PRESTO									
	All									
	DOPAMINE AGONISTS									
	Rasagiline 1 mg					Placebo				
	DOPAMINE AGONISTS				Difference of Yes over No (%)	DOPAMINE AGONISTS				Difference of Yes over No (%)
	Yes (N=247)		No (N=133)			Yes (N=241)		No (N=147)		
N	%	N	%	N	%	N	%	N	%	
ACCIDENTAL INJURY	26	10.5	5	3.8	6.8	16	6.6	4	2.7	3.9
INFECTION	19	7.7	4	3.0	4.7	14	5.8	10	6.8	-1.0
DIZZINESS	17	6.9	3	2.3	4.6	12	5.0	7	4.8	0.2
EXTRAPYRAMIDAL SYNDROME	10	4.0	.	.	4.0	14	5.8	4	2.7	3.1
RASH	10	4.0	.	.	4.0	5	2.1	1	0.7	1.4
PERIPHERAL EDEMA	11	4.5	1	0.8	3.7	12	5.0	3	2.0	2.9
HALLUCINATIONS	10	4.0	1	0.8	3.3	3	1.2	5	3.4	-2.2
CONSTIPATION	13	5.3	3	2.3	3.0	3	1.2	5	3.4	-2.2
ABDOMINAL PAIN	12	4.9	3	2.3	2.6	3	1.2	2	1.4	-0.1
ARTHRALGIA	10	4.0	2	1.5	2.5	4	1.7	1	0.7	1.0
PAIN	11	4.5	3	2.3	2.2	8	3.3	5	3.4	-0.1
TENOSYNOVITIS	5	2.0	.	.	2.0	.	.	.	.	.
SKIN DISORDER	5	2.0	.	.	2.0	5	2.1	1	0.7	1.4

*At least 2% difference of Yes over No in the rasagiline 1 mg group

9.17 Number and Percent of Cohort 2 Subjects Reporting AEs by Entacapone Use (Sponsor ISS Table 57)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	PRESTO									
	All									
	ENTACAPONE									
	Rasagiline 1 mg					Placebo				
	ENTACAPONE				Difference of Yes over No (%)	ENTACAPONE				Difference of Yes over No (%)
	Yes (N=49)		No (N=100)			Yes (N=61)		No (N=98)		
N	%	N	%	N	%	N	%	N	%	
INFECTION	10	20.4	7	7.0	13.4	4	6.6	15	15.3	-8.7
DYSKINESIA	13	26.5	14	14.0	12.5	9	14.8	7	7.1	7.6
ASTHENIA	7	14.3	4	4.0	10.3	4	6.6	12	12.2	-5.7
ARTHRALGIA	7	14.3	5	5.0	9.3	1	1.6	3	3.1	-1.4
WEIGHT LOSS	7	14.3	7	7.0	7.3	1	1.6	3	3.1	-1.4
DIZZINESS	7	14.3	7	7.0	7.3	4	6.6	11	11.2	-4.7
ELECTROCARDIOGRAM ABNORMAL	3	6.1	.	.	6.1	.	.	1	1.0	-1.0
MYASTHENIA	3	6.1	.	.	6.1	2	3.3	.	.	3.3
ANOREXIA	4	8.2	4	4.0	4.2	.	.	1	1.0	-1.0
ABNORMAL VISION	3	6.1	2	2.0	4.1	1	1.6	.	.	1.6
CEREBROVASCULAR ACCIDENT	2	4.1	.	.	4.1	.	.	.	.	.
ALBUMINURIA	2	4.1	.	.	4.1	.	.	1	1.0	-1.0
GINGIVITIS	2	4.1	1	1.0	3.1	.	.	1	1.0	-1.0
JOINT DISORDER	2	4.1	1	1.0	3.1	1	1.6	2	2.0	-0.4
PARESTHESIA	3	6.1	4	4.0	2.1	3	4.9	1	1.0	3.9
ANEMIA	2	4.1	2	2.0	2.1	2	3.3	2	2.0	1.2
URINE ABNORMALITY	2	4.1	2	2.0	2.1	2	3.3	1	1.0	2.3

*Above 2% difference of Yes over No in the rasagiline 1 mg group

9.18 Number and Percent of Cohort 2 Subjects Reporting AEs by Amantadine Use (Sponsor ISS Table 58)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	LARGO and PRESTO										
	All										
	AMANTADINE HYDROCHLORIDE										
	Rasagiline 1 mg					Placebo					
	AMANTADINE HYDROCHLORIDE				Difference of Yes over No (%)	AMANTADINE HYDROCHLORIDE				Difference of Yes over No (%)	
	Yes (N=95)		No (N=285)			Yes (N=99)		No (N=289)			
N	%	N	%	N		%	N	%			
DYSKINESIA	15	15.8	24	8.4	7.4	5	5.1	20	6.9	-1.9	
EXTRAPYRAMIDAL SYNDROME	6	6.3	4	1.4	4.9	6	6.1	12	4.2	1.9	
DRY MOUTH	6	6.3	7	2.5	3.9	1	1.0	6	2.1	-1.1	
VOMITING	6	6.3	7	2.5	3.9	1	1.0	3	1.0	-0.0	
DYSPEPSIA	5	5.3	6	2.1	3.2	2	2.0	7	2.4	-0.4	
DEPRESSION	6	6.3	9	3.2	3.2	2	2.0	15	5.2	-3.2	
AV BLOCK FIRST DEGREE	3	3.2	1	0.4	2.8	.	.	2	0.7	-0.7	
DIZZINESS	7	7.4	13	4.6	2.8	7	7.1	12	4.2	2.9	
DYSPNEA	4	4.2	4	1.4	2.8	.	.	5	1.7	-1.7	
CYST	2	2.1	.	.	2.1	.	.	1	0.3	-0.3	
GASTROINTESTINAL DISORDER	2	2.1	.	.	2.1	1	1.0	1	0.3	0.7	
ALBUMINURIA	2	2.1	.	.	2.1	.	.	1	0.3	-0.3	
PROSTATIC DISORDER	2	2.1	.	.	2.1	1	1.0	2	0.7	0.3	
NAUSEA	8	8.4	18	6.3	2.1	3	3.0	20	6.9	-3.9	

*At least 2% difference of Yes over No in the rasagiline 1 mg group

9.19 Number and Percent of Cohort 2 Subjects Reporting AEs by Antidepressant Use* (Sponsor ISS Table 59)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	LARGO and PRESTO										
	All										
	ANTIDEPRESSANTS										
	Rasagiline 1 mg					Placebo					
	ANTIDEPRESSANTS				Difference of Yes over No (%)	ANTIDEPRESSANTS				Difference of Yes over No (%)	
	Yes (N=52)		No (N=328)			Yes (N=79)		No (N=309)			
N	%	N	%	N		%	N	%			
ACCIDENTAL INJURY	9	17.3	22	6.7	10.6	9	11.4	11	3.6	7.8	
ABDOMINAL PAIN	5	9.6	10	3.0	6.6	1	1.3	4	1.3	-0.0	
ANOREXIA	4	7.7	4	1.2	6.5	.	.	2	0.6	-0.6	
CONSTIPATION	5	9.6	11	3.4	6.3	2	2.5	6	1.9	0.6	
DYSTONIA	4	7.7	5	1.5	6.2	1	1.3	2	0.6	0.6	
BACK PAIN	4	7.7	8	2.4	5.3	3	3.8	12	3.9	-0.1	
SOMNOLENCE	4	7.7	8	2.4	5.3	2	2.5	7	2.3	0.3	
DIZZINESS	5	9.6	15	4.6	5.0	6	7.6	13	4.2	3.4	
DRY MOUTH	4	7.7	9	2.7	4.9	1	1.3	6	1.9	-0.7	
DEPRESSION	4	7.7	11	3.4	4.3	11	13.9	6	1.9	12.0	
HYPERKINESIA	2	3.8	.	.	3.8	.	.	1	0.3	-0.3	
POSTURAL HYPOTENSION	4	7.7	14	4.3	3.4	1	1.3	4	1.3	-0.0	
SINUSITIS	2	3.8	2	0.6	3.2	.	.	5	1.6	-1.6	
ANEMIA	2	3.8	3	0.9	2.9	2	2.5	2	0.6	1.9	
VOMITING	3	5.8	10	3.0	2.7	1	1.3	3	1.0	0.3	
SKIN BENIGN NEOPLASM	2	3.8	4	1.2	2.6	3	3.8	2	0.6	3.2	
ABNORMAL DREAMS	2	3.8	6	1.8	2.0	.	.	3	1.0	-1.0	

*At least 2% difference of Yes over No in the rasagiline 1 mg group

9.20 Number and Percent of Cohort 2 Subjects Reporting AEs by SSRI Use (Sponsor ISS Table 60)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	PRESTO									
	All									
	Rasagiline 1 mg					Placebo				
	SSRI		Difference of Yes over No (%)			SSRI		Difference of Yes over No (%)		
	Yes (N=23)	No (N=126)				Yes (N=36)	No (N=123)			
N	%	N	%		N	%	N	%		
ACCIDENTAL INJURY	7	30.4	19	15.1	15.4	4	11.1	12	9.8	1.4
DEPRESSION	4	17.4	3	2.4	15.0	4	11.1	6	4.9	6.2
ANOREXIA	4	17.4	4	3.2	14.2	.	.	1	0.8	-0.8
BACK PAIN	3	13.0	5	4.0	9.1	3	8.3	7	5.7	2.6
DRY MOUTH	3	13.0	6	4.8	8.3	.	.	5	4.1	-4.1
VOMITING	3	13.0	7	5.6	7.5	1	2.8	1	0.8	2.0
DYSTONIA	2	8.7	2	1.6	7.1	1	2.8	1	0.8	2.0
SINUSITIS	2	8.7	2	1.6	7.1	.	.	5	4.1	-4.1
POSTURAL HYPOTENSION	3	13.0	10	7.9	5.1	1	2.8	4	3.3	-0.5
CONSTIPATION	3	13.0	10	7.9	5.1	1	2.8	7	5.7	-2.9

*Above 5% difference of Yes over No in the rasagiline 1 mg group since one patient in the rasagiline 'Yes' group represents 4.3% of the patients

* Antidepressants used by Cohort 2 members included amitriptyline (rasagiline 5.0%, placebo 8.8%), citalopram (rasagiline 1.1%, placebo 1.5%), clomipramine (rasagiline 0.3%, placebo n=0), doxepin (rasagiline n=0, placebo 0.3%), imipramine (rasagiline n=0, placebo 0.3%), mianserin (rasagiline 0.3%, placebo 0.3%), mirtazapine (rasagiline n=0, placebo 0.3%), nefazodone (rasagiline 0.3%, placebo n=0), paroxetine (rasagiline 2.9%, placebo 3.4%), sertraline (rasagiline 2.1%, placebo 4.4%), desyrel (rasagiline 2.1%, placebo 2.8) and venlafaxine (rasagiline 0.3, placebo n=0) (Sponsor ISS Post-Text Table 54).

9.21 Concomitant use of Anxiolytic, Sedative, Hypnotic and Neuroleptic Agents in LARGO and PRESTO (Sponsor Post-Text Table 96)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	LARGO and PRESTO										
	All										
	ANXIOLYTIC, SEDATIVE, HYPNOTIC, NEUROLEPTIC					ANXIOLYTIC, SEDATIVE, HYPNOTIC, NEUROLEPTIC					
	Rasagiline 1 mg					Placebo					
	Yes (N=82)		No (N=298)			Difference of Yes over No (%)	Yes (N=99)		No (N=289)		
N	%	N	%	N	%		N	%	N	%	
DEPRESSION	9	11.0	6	2.0	9.0	8	8.1	9	3.1	5.0	
ANXIETY	4	4.9	3	1.0	3.9	7	7.1	6	2.1	5.0	
NAUSEA	8	9.8	18	6.0	3.7	9	9.1	13	4.8	4.2	
PAIN	5	6.1	9	3.0	3.1	2	2.0	11	3.8	-1.8	
DIZZINESS	6	7.3	14	4.7	2.6	8	8.1	11	3.8	3.3	
DYSKINESIA	10	12.2	29	9.7	2.5	11	11.1	13	4.8	6.3	
HERPES SIMPLEX	2	2.4	.	.	2.4	.	.	.	.	.	
BACK PAIN	4	4.9	8	2.7	2.2	6	6.1	9	3.1	2.9	
PERIPHERAL EDEMA	4	4.9	8	2.7	2.2	4	4.0	14	4.8	-3.8	
SURGERY & PROCEDURES	2	2.4	1	0.3	2.1	.	.	.	.	.	
SYNCOPE	2	2.4	1	0.3	2.1	1	1.0	2	0.7	0.3	
GASTROENTERITIS	2	2.4	1	0.3	2.1	1	1.0	1	0.3	0.7	
GINGIVITIS	2	2.4	1	0.3	2.1	.	.	1	0.3	-0.3	
CONFUSION	2	2.4	1	0.3	2.1	1	1.0	2	0.7	0.3	

9.22 Summary of Melanoma Cases (Adapted from Sponsor Table 3, ISS Appendix 18.3)

Table 3. Description of melanoma cases in rasagiline clinical program

	Patient no.	Age/sex	Study no.	Tx group	Previous DermExam	Type and location	Exposure at diagnosis	Number of risk factors
1	164	73/M	232 pc	2 mg	no	Invasive, grade IV forehead	2.5 m	7
2	113	74/M	232 act.	2 mg	no	In situ- right lower scapular area	12 m	4
3	246	56/F	233	2 mg	no	In situ- left arm	16 m	4
4	009	49/F	233	1 mg	no	Invasive, grade IV, back	31 m	2
5	064	69/M	233	1 mg	no	In situ -shoulder. Invasive- left check	35 m. 55 m	8
6	036	79/M	233	2 mg	no	In situ- left face	41 m	4
7	494	75/M	135	1 mg (prev. placebo)	no	In situ- upper left back	5 m	6
8	520	78/F	135	1 mg	no	In situ-right back	9 m	2
9	169	74/M	133 pc	1 mg	yes	In situ- right check	6 m	1
10	613	60/M	133 pc	1 mg	yes	In situ- right lower back	6 m	4
11	424	47/F	135	1 mg	no	Invasive-left lower thigh	7 m	3
12	209	57/M	133 pc	0.5 mg	no	Invasive-left medial calf	6 m	4
13	271	68/M	135	0.5 mg	yes	Invasive- left flank	14 m	4
14	544	68/F	233	2 mg	yes	Invasive- right upper arm	3.9 y	4
15	116	53/M	233	1 mg	no	In situ- left medial calf	3.5 y	1
16	16431	74/M	122	Prior Tx	no	Invasive- left scapular	0	3
17	41604	73/M	122 pc	placebo	yes	In situ-back trunk	0	3
18	141611	73/M	122	Prior Tx	no	In situ- right suprascapular area	0	2
19	756	66/M	133	Prior Tx	no	In situ -left check	0	3

pc = placebo controlled

Act. = active phase

9.23 Information from SEER Registries on in situ Melanoma

9.23.1 Kentucky Cancer Registry Website (<http://www.kcr.uky.edu/history.html>)

“All Kentucky acute care hospitals and their associated outpatient facilities are required to report each case of cancer using the Cancer Patient Data Management System (CPDMS) developed by KCR. The larger hospitals (those diagnosing or treating more than 100 new primary cancer cases annually) are required to have their own tumor registrar(s)...In 1994, the legislation requiring reporting of cancer cases was modified to include reporting from all health care facilities that either diagnose or treat cancer patients. These additional facilities include freestanding treatment centers, non-hospital (private) pathology laboratories, and physician offices.”

9.23.2 Atlanta Cancer Registry Website

(<http://www.sph.emory.edu/GCCS/GCCSdata/STGGWI/BLADSTG.htm>)

Tabular data presented in the Atlanta registry website notes that for all cases of melanoma reported in Caucasian patients, 24.4% were in situ, 62% were localized, 2.5% were regional, 0.8% were distant and 10.3% were of unknown stage.

9.24 Summary of Published Case Reports of Melanoma with Levodopa Usage

Case No.	Age/Sex	Site Primary Melanoma	Prior nevus at melanoma site	Time from Rx L-dopa to melanoma diagnosis or recurrence	Time from Dx melanoma to Rx L-dopa	Authors advice on L-dopa use in pts. with melanoma hx.
1	55/M	Skin	>6 mo	4 mo	4 yr	?
2	50/M	Skin	Since birth	9 mo	0	No
3	70/M	Skin	20 yr	(18 mo)	N/A	No
4	62/M	Skin	Unknown	3 mo	1 yr	No
5	62/M	Skin	Unknown	No recurrence	2 yr	No
6	71/M	Skin	No	(L-dopa withheld)		No
7	--	--	Unknown	(L-dopa withheld)		Caution
8	--	--	Unknown	(8 yr)	N/A	Caution
9	48/M	Skin	15 yr	(6 yr)	N/A	Yes
10	74/F	Skin	Unknown	(10 yr)	N/A	No
11	69/F	Choroid	No	(7 yr)	N/A	?
12	53/F	Choroid	No	(4 yr)	N/A	?
13	70/F	Ciliary Body	No	(1 yr)	N/A	?
14	67/M	Choroid	No	(1 yr)	N/A	?
15	58/M	Skin	Since birth	(14 mo)	N/A	Caution
16	72/M	Skin	15 yr	(5 yr)	N/A	No
17	67/M	Skin	No	(18 mo)	N/A	Yes
18	66/F	Skin	Unknown	(11 yr)	N/A	Yes
19	65/F	Mets	N/A	(9 yr)	N/A	Yes
20	59/F	Skin	>45 yr	(5 mo)	N/A	No
21	38/M	Skin	Unknown	No recurrence	12 yr	Yes

The table above was adapted from Weiner et al., Neurology 1993;43:675. It does not include all case reports that have been published in the literature, which are estimated to be approximately 50, over the period from 1970 to 2000. Additional details are given in section 3.3.4.2.1 of this report.

9.25 Age-Adjusted Background Melanoma Rates by Country for Clinical Sites from TEMPO, LARGO and PRESTO

Age-Standardized melanoma rate (from 1997 to 2000) for geographic locations of clinical sites within the LARGO, PRESTO and TEMPO

Study	Country of Study Site ¹⁵⁵	# of Subjects	Age-Standardized Melanoma Incidence Rate per 100,000 (From years between 1996 - 2000)	
			Male	Female
LARGO ¹⁵⁶	Argentina	141	1.2 **	2.3**
	Austria	16	12.4	15.6
	Belgium ¹⁵⁷	3	6.7	6.5
	France	25	4.1	6.2
	Germany	11	5.0	5.3
	Hungary	87	8.3	7.3
	Israel ¹⁵⁸	54	9.6	9.8
	Italy (Genoa)	141	5.2	5.8
	Netherlands	25	6.9	9.8
	Portugal	17	2.6	3.6
	Romania	104	3.4	3.3
	Spain (Zaragoza)	21	2.3	3.3
	UK (Oxford Region)	42	5.8	7.6
PRESTO	Canada, Alberta	14	7.5	7.5
	Canada, Saskatchewan	3	8.0	7.6
	Canada, Ontario	17	9.6	8.0
	Canada, Quebec	20	3.7	3.3
	US ^{159*}	418	Median: 19.0 Range: 16.6 – 24.4	Median: 12.1 Range: 9.9 – 13.4
TEMPO	Canada, Alberta	9	7.5	7.5
	Canada, Saskatchewan	12	8.0	7.6

¹⁵⁵ Within the Parkin reference, some countries presented melanoma rates by region rather than the country as a whole. The area in parentheses represents the locale of the melanoma rate displayed in the table. An attempt was made to pick the most appropriate region based upon the location of the study sites, however the presence of multiple study sites and a limited list of regions within the reference made this difficult.

¹⁵⁶ Information on site and number of participants from Section 10.3.1, pg. 88, LARGO study report

¹⁵⁷ Melanoma statistics for Belgium, Hungary, Portugal and Romania are IARC 1995 age-adjusted rates per 100,000 from at <http://www-dep.iarc.fr/europe95/inc/ASRbarinc.pdf>

¹⁵⁸ Rates were available for several populations and sub-populations within Israel, and the rate displayed in the Table reflects that of the total Jewish population

¹⁵⁹ Taken from the CDC/NCI state cancer profiles at <http://statecancerprofiles.cancer.gov/cgi-bin/incidencrates/incidencrates.pl?00&053&00&0&1&1&1>

	Canada, Ontario	26	9.6	8.0
	US**	157	Median: 19.0 Range: 13.8 – 21.8	Median: 12.4 Range: 8.7 – 13.4

<http://sttcancerprofiles.cancer.gov/cgi-bin/incidencerates/incidencerates.pl?00&053&00&0&1&1&1>

* PRESTO included the following states and territories within the United States: Arkansas, California, Colorado, Connecticut, Florida, Georgia, Indiana, Mexico, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Puerto Rico, Rhode Island and Virginia

** TEMPO included the following state: Alabama, Arizona, Connecticut, Georgia, Florida, Illinois, Kansas, Massachusetts, Nebraska, New Jersey, New York, Kansas, Ohio, Pennsylvania and Virginia

9.26 Calculations of Melanoma Rates in other Parkinson's Disease Therapy Trials

Melanoma Cases:

For controlled trials and extensions, both the summary and the patient files were checked for cases of melanoma (variable names checked include: MRI, MI, MPC, MAC, RIDX, RANDX, DDATE, DD30 and EXTDX)

Person-Years:

Person-years for the controlled trial data was obtained by subtracting the date of the first dose of randomized treatment (variable name: FDRAN) from date of last randomized treatment (variable name: LDRAN) for each of the participants, and then summing the results.

Person-years for the extension trials were calculated by subtracting the date of the first dose of extension treatment (variable name: FDEX) from the date of the last dose of extension treatment (variable name: LDEX) for each of the subjects in the extension trial patient file, and summing the results (variable name: PerYears)

9.27 Melanoma Summaries from other Parkinson's Disease Development Programs

1. Orion (entacapone) submitted data on 1,303 participants (806 entacapone and 497 placebo) from five placebo-controlled trials (698 PYs total for both entacapone and placebo) investigating entacapone as an adjunct-therapy to levodopa, and 899 participants from six extension trials (1788 PYs total).

No cases of melanoma occurred in the individual trials reported in the electronic datasets. The sponsor notes that one report of malignant melanoma was identified from the Orion Pharma Drug Safety (OPDS) database. However, as this participant was from a study not included in the trials (person-time) submitted by the sponsor, this case was disregarded.

2. Pharamcia & Upjohn (pramipexole) submitted data on 19 controlled clinical trials (16 placebo-control/3 active-control, 7 monotherapy/12 levodopa adjunct). These

contained a total of 3001 participants for whom both treatment start and stop dates were recorded, for a total of 2096 PYs: 1572 pramipexole subjects (1048 PYs), 1195 placebo subjects (452 PYs), 150 carbidopa-levodopa subjects (545 PYs), and 84 bromocriptine subjects (51 PYs). Data was also submitted for 2880 participants in 13 extension trials (4813 PYs).

A total of 11 cases of melanoma were reported during the pramipexole development program, although for one subject the date of diagnosis preceded the date of first study drug by 99 days. Details of the melanoma cases are summarized below:

Table 1: Characteristics of melanoma cases during pramipexole clinical development

Patient ID #	Age/ Sex	Trial ID # *	Study Location	Tx Group (RCT/Extension)	Levo -dopa?	Days to dx**	Dx'ed RCT or Ext?
7	59/M	0014	Non-North America	Pramipexole	Yes	161	Ext
2285	64/M	0002	North America	Placebo/Pramip.	Yes	-99	RCT
2342	73/M	0002	North America	Pramipexole	Yes	422	Ext
1273	73/M	0052	Multiple ***	Pramipexole	Yes	225	RCT
2075	65/M	0002	North America	Pramipexole	Yes	569	Ext
2109	75/M	0002	North America	Pramipexole	Yes	1191	Ext
2201	61/F	0002	North America	Placebo/Pramip.	Unk.	1225	Ext
2254	70/M	0002	North America	Pramipexole	No	1212	Ext
127	52/M	0072	North America	Levodopa	Yes	385	RCT
140	74/M	0072	North America	Pramipexole	No	693	RCT
1	60/M	0072	North America	Pramipexole	No	1427	RCT

*Prefix for all trials ID numbers: M/2730/

**Days since beginning of trial to diagnosis with melanoma. In one case (italicized) the diagnosis date provided occurred before the start date of the RCT.

*** Contained study centers both inside and outside North America

3. GlaxoSmithKline (ropinirole) submitted data from 13 controlled trials (9 placebo-controlled/4 active-control, 6 monotherapy/7 as a levodopa adjunct). The trials contained 2238 participants (with both study drug start and stop dates) for a total of 2846 PYs: 1360 ropinirole (1688 PYs), 356 bromocriptine (447 PYs), 332 placebo (207 PYs), and 190 levodopa (504 PYs). Data was also submitted for 900 subjects in nine extension trials (531 PYs total).

One case of melanoma was identified, occurring in a ropinirole-treated participant in a controlled clinical trial.

Table 2. Characteristics of melanoma cases during ropinirole clinical development

Patient ID #	Age/ Sex	Trial ID #	Study Location	Tx Group (RCT/Extension)	Levo -dopa?	Days to dx*	Dx'ed RCT or Ext?
125.031 .00698	51/M	125	Multiple **	Ropini/ropinirol	No	420	RCT

*Days since start of study drug (beginning of RCT) to diagnosis with melanoma

** Contained study centers both inside and outside North America

4. Hoffman-LaRouche (tolcapone) submitted data from eight controlled trials (three placebo-controlled) involving 545 person-years and nine extension trials involving 2655 person-years. A total of 33 cases of melanoma were recorded among the 1450 controlled trial and 1397 extension study participants. These cases are summarized in the table below.

Table 3. Characteristics of melanoma cases during tolcapone clinical development

Patient ID #	Age/ Sex	Trial ID #	Study Location	Tx Group (RCT/Ext.)	Levo -dopa?	Days to dx*	Dx'ed RCT or Ext?
14586/ 0126	73/M	14654	North America	Tolcapone/Tolc	Yes	244	RCT
14671/ 0211	69/M	14655	Non-North America	Tolcapone/Tolc	Yes	35	RCT
14059/ 0372	81/M	14653	North America	Placebo	Yes	54	RCT
14065/ 0076	64/M	14653	North America	Tolcapone/Tolc	Yes	43	RCT
14134/ 0182	75/M	14653	North America	Tolcapone/Tolc	Yes	74	RCT
11900/ 902	51/F	14114	Non-North America	Placebo/Tolc.	Yes	537*	Ext.
11980/ 1401	65/F	14115	Non-North America	Placebo/Tolc.	Yes	213*	Ext.
11980/ 1402	82/M	14115	Non-North America	Tolcapone/Tolc	Yes	334*	Ext.
12809/ 0015	69/M	14316	North America	Tolcapone/Tolc	Yes	258*	Ext.
12848/ 0202	70/M	14316	North America	Placebo/Tolc.	Yes	574*	Ext.
12849/ 0103	72/M	14316	North America	Tolcapone/Tolc	Yes	1055*	Ext
12849/ 0118	74/M	14316	North America	Placebo/Tolc.	Yes	713*	Ext.
14057/ 0432	66/M	14653	North America	Tolcapone/Tolc	Yes	64*	Ext.
14582/ 0039	67/M	14654	North America	Placebo/Tolc.	Yes	122*	Ext.
14584/	66/M	14654	North	Tolcapone/Tolc	Yes	366	Ext.

0096			America				
14588/ 0002	57/M	14654	North America	Tolcapone/Tolc	Yes	844*	Ext.
14644/ 0224	64/M	14654	North America	Tolcapone/Tolc	Yes	428*	Ext.
15224/ 0066	75/F	14656	Non-North America	Tolcapone/Tolc	Yes	840*	Ext.
15228/ 0403	72/F	14656	Non-North America	Bromocriptine/ Tolcapone	Yes	8*	Ext.
15301/ 0200	53/F	14657	Non-North America	Tolcapone/ Tolcapone	Yes	187*	Ext.
15342/ 4016	60/M	14657	Non-North America	Tolcapone/Tolc	Yes	445*	Ext.
15393/ 0516	68/M	14657	Non-North America	Tolcapone/Tolc	Yes	470*	Ext.
15396/ 0805	76/F	14657	Non-North America	Tolcapone/Tolc	Yes	315*	Ext.
15396/ 0813	64/F	14657	Non-North America	Tolcapone/Tolc	Yes	337*	Ext.
15400/ 2518	78/F	14657	Non-North America	Tolcapone/Tolc	Yes	577*	Ext.
15413/ 4605	54/M	14657	Non-North America	Tolcapone/Tolc	Yes	306*	Ext.
15413/ 4610	55/M	14657	Non-North America	Tolcapone/Tolc	Yes	258*	Ext.
15923/ 0131	77/F	14971	North America	Tolcapone/Tolc	Yes	210*	Ext.
15930/ 0075	68/M	14971	North America	Tolcapone/Tolc	Yes	688*	Ext.
15930/ 0079	65/M	14791	North America	Tolcapone/Tolc	Yes	216*	Ext.
15932/ 0147	52/M	14971	North America	Tolcapone/Tolc	Yes	868*	Ext.
15937/ 0307	74/M	14971	North America	Tolcapone/Tolc	Yes	312*	Ext.
15939/ 0349	71/M	14971	North America	Tolcapone/Tolc	Yes	753*	Ext.

*Calculated from first date of the extension study only (did not include RCT time)

5. Lilly (pergolide) submitted data from five controlled trials which included a total of 942 subjects who accumulated 930 person-years. No cases of melanoma were reported during the pergolide development program.

9.27 Construction of the Post-Screening Rasagiline Dataset

The following files within the NDA (crt/datasets) were concatenated in order to create the master file for analysis. The constituent files were the MRF (melanoma risk factors) for:

File Name	Study	N in MRF File

TVP-1012-232-MRF	TEMPO	21
TVP-1012-233-MRF	TEMPO Extension	212
TVP-1012-122-MRF	LARGO	471
TVP-1012-133-MRF	PRESTO	346
Total		1050

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9.28 Biopsy-Confirmed Melanomas Among all Persons Screened for the American Academy of Dermatology Screening Program, 1992-1994

	Invasive Melanoma				In Situ Melanoma							
	Men		Women		Men		Women					
	Case	Screened	Rate*	Case	Screened	Rate*	Case	Screened	Rate*			
<45	19	26537	71.6	30	51253	58.5	6	26537	22.6	7	51253	13.7
45-54	29	16455	176.2	19	26192	72.5	13	16455	79.0	13	26192	49.6
55-64	34	19952	170.4	20	27837	71.8	14	19952	70.2	9	27837	32.3
65-74	52	25309	205.5	25	31090	80.4	20	25309	79.0	7	31090	22.5
75+	13	7763	167.5	15	9986	150.2	4	7763	51.5	4	9986	40.1

* Cases per 100,000 persons screened.

DRAFT

9.29 Sources of Sponsor Data Presented Within the Review of Systems (ROS)

Cohort 1 (rasagiline monotherapy):

- *SAEs*: ISS Post-Text Table 85
- *Discontinuations*: ISS Post-Text Table 94
- *AEs*: ISS Post-Text Table 68

Cohort 2 (rasagiline as levodopa adjunct):

- *SAEs*: ISS Post-Text Table 86
- *Discontinuations*: ISS Post-Text Table 95
- *AEs*: ISS Post-Text Table 69

Cohort 9 (all PD patients exposed to rasagiline):

- *SAEs*: 120 Day Safety Update ISS Post-Text Table 46
- *Discontinuations*: 120 Day Safety Update ISS Post-Text Table 47
- *AEs*: 120 Day Safety Update ISS Post-Text Table 36

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

M. Lisa Jones
6/25/04 04:07:35 PM
MEDICAL OFFICER

Judith Racoosin
6/27/04 12:51:44 PM
MEDICAL OFFICER
See my memo for comment on specific safety issues
including melanoma, as well as some edits to
Dr. Jones proposed labeling.