Memorandum

To: File – NDA 21-641

From: Director, ODE1

Date: August 12, 2005

Subject: NDA 21-641 (Rasagiline for Parkinson's Disease)

There are two principal issues that the Division, including Dr. Katz, believe should delay approval of rasagaline at this time, pending either further explanation or further studies: 1) the adequacy of assessment of potential tyramine reactions to the 1 mg dose of rasagiline, and 2) the possibility that rasagaline increases the rate of melanomas.

1. Tyramine Reaction

A variety of defects in the tyramine challenge test and other studies conducted by the sponsor were identified (lack of BP response at the high does of 800mg tyramine in the challenge test, not our experience in these tests; in other studies tyramine was given with, or close to, a meal, almost surely delaying absorption so that a test of a very high blood level was not accomplished) and described by Drs. Kapcala, Feeney, and Katz, leading them to the conclusion that a potential tyramine reaction (perhaps in people who took a 1A2 inhibitor) to the 1mg therapeutic dose could not be ruled out. They believe the drug could be approved with labeling warning of possible tyramine reactions (not agreeable to the sponsor) but that it could not yet be given a clean, "MAO-B" selective bill of health.

I agree with these conclusions; to claim MAO-B selectivity, TEVA should perform the thorough study described in the 9/5/03 approvable letter or the alternative study suggested.

2. Melanoma

The melanoma issue is difficult and complex, as I will describe. Initially, in our approvable letter, we indicated that the possible increased melanoma risk would not preclude approval and that a large controlled trial to evaluate this potential further could be conducted after marketing. Part of the basis for our concern was a single melanoma in the albino rat carcinogenicity

study, a tumor thought almost never to occur in these animals. It is now fairly clear that melanomas are not so very rare in these animals (See Dr. Freed's summary), so that the animal data no longer buttress, at least not very much, the concerns raised by human data. Nonetheless, the Division now proposes that the large melanoma study be conducted prior to approval.

The melanoma concern is addressed by several analyses in 2 main categories

1. The rate of melanoma in controlled trials and their extensions in drug-treated and placebo patients.

2. Population analyses: The rate of melanoma in the rasagiline data base compared to rates in data bases of other anti-Parkinson's Disease Drugs; and to rates in the SEER and American Academy of Dermatology (AAD) databases, and to rates in non-rasagiline treated patients with PD (Study EP002)

1. Rasagiline Data Base

The analyses of the rasagiline data base poses many problems. To start, many of the tumors occur too soon to be plausibly drug-induced. In Dr. Jones' Table 1 listing all the melanomas, e.g., 7 of the 18 malignant melanomas on study occurred in < 7 months, with 2 at ≤ 0.35 years (one on placebo), 3 at < 0.5 years, and 2 at 0.6 and 0.54 years. It could be strongly argued that those 7 are very implausibly related to the drug.

There were also 3 cases found at baseline screening. Dr. Jones (p 15) omits those as not being "treatment emergent" but they seem about as treatment emergent as tumors discovered at 0.167 years, 0.35 years and generally , 6 months, which were surely present (but missed) at baseline, so omitting them does not seem obviously correct; at least it's not the only way to consider these. If there are counted with the placebo group the rate/patient year on drug and placebo is quite similar.

The attempt to display D/R was not simple, as doses varied, so that 3 displays were used: by modal dose, the dose at time of tumor discovery, and the patient's highest dose. The following tables (all courtesy Dr. Jones) show the results for modal dose and dose at diagnosis, broken into invasive and noninvasive (in situ) melanomas. All tables show the number of melanomas, both invasive, in situ, and total, and the rate per 100,000 patient years in parentheses. As noted, 3 tumors found at baseline are not included as placebo cases (as the sponsor had proposed) in the tables below. I have shown the effect of including them (as was done in Dr. Jones' Table 3 (from the sponsor) in my Table 1 and also shown data in table 2 (dose at time of diagnosis) removing the 7 "implausibly early" tumors (≤ 0.7 years).

Table 1: Modal Dose

No of Cases (Cases/ 100,000 PYs)

	0 mg	0.5 mg	1 mg	2 mg
Invasive	0	2 (677)	5 (327)	1 (185)
In situ	1 (238)	0	6 (393)	3 (554)
Total	1 (238)	2 (677)	11 (720)	4 (738)

If 3 tumors at baseline (2 in situ, one invasive) are added to the 0 column, we get

	0 mg	0.5 mg	1 mg	2 mg
Invasive	1 (238)	2 (677)	5 (327)	1 (185)
In situ	3 (713)	0	6 (393)	3 (554)
Total	4 (951)	2 (677)	11 (720)	4 (738)

Table 2: Dose at Diagnosis

	0 mg	0.5 mg	1 mg	2 mg
Invasive	0	2 (677)	5 (327)	1 (185)
In situ	1 (238)	0	7 (438)	2 (369)
Total	1 (238)	2 (677)	12 (785)	3 (554)

Based on Dr. Jones' Table 1, I removed 7 cases (1 placebo, 6 rasagiline) that occurred implausibly early. I did not add baseline tumors to this table.

	0 mg	0.5 mg	1 mg	2 mg
Invasive	0	1 (339)	4 (262)	0
In situ	0	0	4 (262)	2 (369)
Total	0	1 (339)	8 (523)	2 (369)

On p 15 Dr. Jones suggests, discussing (her table 4) (my table 1) that there is a "potential dose-response relationship for total melanomas" but I don't think that is so for the total tumors. Moreover, in situ tumors rise (somewhat) with dose while invasive ones decline (somewhat) with dose, not too plausible. In looking at her Table 5, based on highest dose, which gives results similar to my Tables 1 and 2 (her tables 4 and 6). Dr. Jones says "as with the modal dose-response table, increasing dose does not demonstrate a pattern of increasing melanoma occurrence." I think

the second statement is correct and note that removing early tumors (as well as the baseline tumors), also shows no dose-response.

Considering late tumors (second part of my table 2), there are none on placebo and some on drug. That is because no one received placebo beyond 6 months. There are therefore no placebo-controlled data to answer the critical question concerning tumor rates during what seems like the most relevant time (late). To analyze the relevant data as best we can we will need to look at the tumor rate over time. I believe the correct analysis here would be to show Kaplan-Meir curves for tumor over time (all drug doses vs placebo, recognizing placebo only last 6 months). One would probably have to look separately at patients subjected to careful screening vs others (earlier patients). Certainly, one would expect to see an increased rate over time in the treated patients if rasagiline were causing melanomas to occur.

All in all, I find this aspect of the analysis, i.e., within the total rasagiline database, not very persuasive. Melanomas are reasonably common at baseline and within a few months of treatment (very unlikely to be drug-induced) and about half of the tumors seen (3 baseline, 7 within 0.6 years) occur in this period.

2. Cohort Analyses

A variety of comparisons were made and all of them reflect the difficulties of observational data, including potential differences in intensity of observation, potential selection bias in identifying patients for study, differences in populations and geographic locations Melanoma rates on rasagiline were compared with the SEER data base (Surveillance, Epidemiology, and End Results Cancer Registry of the US NCI), TEVA's study EPOO2, a North American study of people with PD <u>not</u> receiving rasagaline in which patients were screened once for melanoma, both by medical history and examination, and the American Academy of Dermatology (AAD) Screening program. The most relevant comparison would seem to be between the rasagiline data base and study EPOO2.

Study EPOO2 found, for newly identified melanomas (Dr. Jones considered the historical part of the study unreliable and, in any case, it was the dermatologic screen that was most comparable to AAB and to the rasagiline studies), 20 in situ and 4 invasive tumors, a rate of 1.1% (0.9% in situ, 0.2% invasive). This 1.1% was 18.3 times the rate in SEER and 6.9 times the rate in a SEER subset of comparable age and sex. This is possibly a small overestimate as melanoma rates have been rising since the SEER data were collected in 1999. The sponsor thinks the comparison suggests an increased rate of melanoma in PD, which, of course, could also relate to other treatments.

Our approvable letter asked for a comparison of EPOO2 with the AAD database, a data base with search efforts far more similar to the rasagiline data than

SEER, and to an analysis of results by age. (As Dr. Jones' Table 8 (p 22) shows, rates appear to rise with age, although they are pretty stable from 55 on). As Dr. Katz and Jones point out, the AAD data may underestimate the rate of melanoma. The AAD data were collected 1992-4; SEER suggests a roughly 28% increase since then; the AAD data thus may be an underestimate; on the other hand, inclusion of Canadian centers in EPOO2 could lead to underestimation of the melanoma rate in the PD population.

The results of the comparison of EPOO2 to AAD (Jones' Table 11) show a substantial increase rate of in situ melanomas.

Table 3

Type	Observed	Expected (AAD)	O/E	95% CI
Invasive	4	3.3	1.2	0.3-3.1
In situ	20	1.2	16.7	10.2-25.7
Total	24	4.5	5.3	3.1-7.9

The sponsor interprets these results as indicating an increased rate of melanoma in PD. As Dr. Katz notes, some of this could relate to time trends in melanoma, but considering that and the Canadian centers in AAD there seems to be an increased rate of melanomas in the EPOO2 population compared to AAD. Acknowledging numerous additional uncertainties of such cohort studies, there certainly is a strong suggestion that PD patients have increased rates of melanoma.

Comparison of the rasagiline data with AAD gives (per Dr. Katz and Jones' Table 12)

	Observed	Expected (AAD)	O/E	95% CI
Invasive	4 *	1.5	2.6	0.72-6.74
In situ	6	0.59	10.2	3.7-22.1

* Melanomas in NA after institution of skin examination for melanoma screening

While at first glance this suggests a strong signal of rasagiline induction of in situ tumors, it does not take into account the results of the EPOO2 vs AAD comparison (above). Although different tumors are included, comparative results seem important.

O/E

EPOO2 vs AAD		Rasagiline vs AAD
Invasive	1.2	2.6
In situ	16.7	10.2
Total	5.3	------

This comparison suggests little of effect of rasagiline on melanoma rates. The increased rates seem attributable to a fairly substantial effect of PD on melanoma, particularly in situ melanoma.

It would probably be useful to compare directly the rasagiline and EPOO2 data, but from the above it seems clear it will not show a rasagiline effect on melanomas. I would therefore conclude, somewhat more strongly than Dr. Katz (p 16) that the overall rasagiline melanoma rates do not seem different from rates in the EPOO2 population. Dr. Jones finds (p 26) these data insufficient to reach a conclusion.

Dr. Katz also refers to previous analyses of melanoma rates on rasagiline before active screening, noting a rate of 5.8 tumors/1000 PYs on rasagiline (but based on just 6 tumors) vs 1.6 tumors/1000 PYs on pramipexole (the highest of the previous data bases). This finding cannot be dismissed, certainly, but we have very small numbers here, and many factors, notably the level of effort devoted to finding the tumors, that could be quite variable.

3. Delayed vs Immediate Start Analyses

(PRESTO and TEMPO trials)

TEMPO compared placebo (n=138) 1 mg/day (n=134), and 2 mg/day (n=132) rasagiline for 6 months, followed by 6 months of active treatment, with patients on rasagiline staying on assigned dose and placebo patients being switched to 2 mg/day. A total of 380 patients entered this second phase (of 404 who started the study). At the end of month 12, patients could go onto open-label extension, initially on 2 mg/day, then 1 mg/day (when 2 mg was shown to have no advantage over 1 mg.

PRESTO was similar, with randomization to placebo (n=159), rasagiline 0.5 mg (n=164) or rasagiline 1 mg (n=149). After 6 months rasagiline patients continued on dose and placebo patients were randomized to 0.5 or 1 mg; 338 patients entered the active treatment phase. Patients could go on 1 mg rasagiline after 12 months.

For the 2 studies, there were 17 total tumors, none of which occurred on placebo. The analysis of delayed vs immediate treatment allows an examination of treatment duration effect, as the delayed treatment patients are always "6 months behind." Note though, that this is only relevant for the late comparison. If one looked at immediate start, patients for 0-6 and 6-12 months, their exposure would be identical to the late start 6-12 and 12-18 months. In fact, overall, in the immediate start group, the rate of melanomas was 15/1345 PY or 11.2 tumors per 1000 PYs while in the delayed start group it was 2/557 PYs or 3.6 tumors per 1000 PYs, with

overlapping 95% CIs. That, at first glance, suggests increasing melanoma rates with increased duration of exposure but, in fact, it's not that simple.

It is critical to look at the distribution of tumors not by immediate vs delayed, but by duration of treatment. Dr. Jones' Table 18 shows rates by duration of rasagiline exposure: Thus, the 0-6 month group shows for the PRESTO immediate group the first 6 months of the study and 6-12 shows the second 6 months of the study. But for the PRESTO delayed group 0-6 shows the second 6 months of the study (but the 1st 6 months of rasagiline) and 6-12 shows the 2nd 6 months of rasagiline but months 12-18 of the study. Thus the groups in 0-6 and 6-12, whether in PRESTO immediate or delayed reflect the same period of exposure.

Number and Risk of Melanoma by Duration

Group	0-6 mos	6-12 mos	12-18 mos	18-24 mos	>24 mos
Number of Melanomas					
PRESTO Immediate	3 (1%)	2 (0.6%)	1 (0.3%)	0	0
PRESTO Delayed	1 (0.6%)	0	0	0	0
TEMPO Immediate	1 (0.4%)	0	2 (0.8%)	0	6 (2%)
TEMPO Delayed	0	0	0	0	1 (0.7%)

In PRESTO, which was the later study, with more attention to dermatologic evaluation, the melanomas were found early, especially in people randomized initially to drug, perhaps because screening began during that period. Bu that does not explain why the delayed group did not show the same rates as the immediate group, once each was receiving rasagiline; thus for the first 12 months of rasagiline exposure those randomized initially to rasagiline showed 5 tumors, while those initially randomized to placebo, but they given rasagiline for the same 12 months, showed only 1. Neither group showed any late tumors. This finding has to be a chance occurrence, as there is no known difference between the groups (and, I'd say) because the tumors seem too early to be plausibly drug-induced).

In TEMPO there were 6 tumors after 24 months in the immediate group, but only one in the delayed group. Exposure was of similar duration but the TEMPO immediate group would always have 6 months more exposure to rasagiline. Finding more tumors in the group with longer exposure has initial plausibility but it is somewhat difficult to believe that the difference of just 6 months can account for the 6 vs 1 finding.

We thus have, in the delayed vs immediate analysis, a finding in PRESTO (5 vs 1 in months 0-12) that cannot represent anything but random noise or unrecognized bias because the only difference between the groups is when exposure began, not duration of exposure, and a finding in TEMPO of essentially identical magnitude that could represent an effect of 6 months longer exposure in the immediate group. The observation that the numbers in the two cases are essentially

the same strongly suggests (to me at least) that both findings represent "noise," random movement, although of course it could be that only the PRESTO finding is noise and the TEMPO finding is real.

To Summarize:

1. The rate of melanoma on rasagiline seems higher than the rate in previous PD data bases, even if only the 6 cases before screening are considered but, of course, any observation based on just 6 tumors has considerable uncertainty associated with it. There is no suggestion of DIR in the data base (I somewhat disagree with Dr. Katz on this) but the rate in all doses is greater than placebo if rate per patient years is considered, unless 3 tumors found at screening counted, as the sponsor urges, in which case rates are about the same.

Use of overall rates/PY does not seem optimal for tumor observations, which could change over time, and an analysis of rate over time is needed, probably with pooled dosage groups. Separate analyses might be done based on screening and observation practices at any given time. One would surely expect to see an increased rate over time (with constant observation behavior) for a drug-induced tumor.

2. Cohort analyses, particularly the rasagiline data base vs EPOO2 (a PD without rasagiline data base) seems to show no effect of rasagiline, a relatively powerful observation, I believe.

3. Delayed vs immediate treatment analysis weakly points to increased rate of melanoma with longer exposure but an equally large difference was seen among groups with identical durations of exposure to rasagiline.

4. The animal data do not appear to include a particularly rare case of melanoma; earlier analysis had suggested that the single melanoma seen was extremely rare.

Conclusion:

For reasons described above, I find the evidence that rasagiline promotes/causes melanomas weak, as does Dr. Katz. Moreover, it is very hard to see the basis in any of the reviews for the change from our pervious position that the drug could be approved with labeling about the melanoma possibility. The main new data (the cohort analyses and EPOO2 are actually reassuring). Nonetheless, on a matter of such importance I want to be sure that the 3 major analyses described here and by Drs. Jones, Feeney and Katz have been fully considered by FDA and the sponsor. I also believe the rasagiline data need to be analyzed by time of exposure, which has not yet been done. I therefore support a second approvable letter with prompt discussion of all of our analyses with the sponsor, who will be asked for their own analyses of any new data and the Kaplan-Meier analyses of tumor rates. Depending on the outcome of these discussions, rasagiline may need to go to an advisory

committee. I think it is likely that we will consider the melanoma issue resolved after these fuller discussions and analyses but I do not believe they are not resolved yet.

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/s/

Robert Temple
8/12/05 02:39:43 PM
MEDICAL OFFICER

CLINICAL REVIEW: RASAGILINE RESPONSE TO APPROVABLE LETTER SAFETY REVIEW

Application Type	NDA
Submission Number	21-641
Submission Code	AZ
Letter Date	November 4, 2004
Stamp Date	November 4, 2004
PDUFA Goal Date	August 4, 2005
Reviewer Name	M. Lisa Jones, MD, MPH
Review Completion Date	July 27, 2005
Established Name	Rasagiline
(Proposed) Trade Name	Agilect®
Therapeutic Class	MAO-B Inhibitor
Applicant	Teva Neuroscience, Inc.
Priority Designation	Standard
Formulation	Oral
Dosing Regimen	1 mg
Indication	Parkinson's Disease
Intended Population	Parkinson's Disease Patients

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1. INTRODUCTION AND BACKGROUND

1.1 Data Sources

1.1.1 Sponsor Documents

1. NDA 21-641 (Rasagiline). Electronic Submissions: Worldwide Regulatory Response to Rasagiline and Response to FDA Reviewer Questions. Prepared by Teva Neuroscience, Inc. Received January 11, 2005 and February 4, 2005.
2. NDA 21-641 (Rasagiline). Amendment to Pending Application: Response to FDA Action Letter. Prepared by Teva Neuroscience, Inc. Dated November 4, 2004.
3. NDA 21-641 (Rasagiline). Electronic Integrated Summary of Safety (ISS) including Post-Text Tables, Electronic Datasets, Electronic Case Report Forms (CRFs), and Appendices. Prepared by Teva Neuroscience, Inc. Dated August 2003.
4. NDA 21-641 (Rasagiline). Electronic 120-Day Safety Update, including ISS with Post-Text Tables. Prepared by Teva Neuroscience, Inc. Dated December 2003.

1.1.2 FDA Documents

1. NDA 21-641 (Rasagiline). NDA Approvable Letter – Misc. Deficiencies and Labeling Revisions Listed in Letter. Prepared by the FDA[1] DNDP[2]. Dated July 2, 2004.
2. NDA 21-641 (Rasagiline). NDA Primary Safety Review. Prepared by M. Lisa Jones, MD, MPH. Dated July 5, 2004.

1.2 Review Content

Rasagiline (Agilect ®) was issued an Approvable Action Letter from the DNDP[2] in July 2004. The Approvable Letter contained requests for further sponsor analysis and information pertaining to unresolved safety questions from the initial NDA review; additionally, the approvable letter included proposed labeling drafted by the Division (see Appendix 12.1 for safety related labeling). Briefly, these safety issues included the following:

1. ***Tyramine***: The DNDP reviewers were not convinced that the selectivity of rasagiline for the B form of the MAO enzyme was adequately demonstrated in the tyramine interaction studies submitted with the original NDA. The sponsor was requested to conduct an additional study of tyramine sensitivity.
2. ***Melanoma***: A total of 24 melanomas (among 22 subjects) were diagnosed during the rasagiline development program: 20 in rasagiline-treated subjects, 1 in a placebo-

[1] FDA=United States Food and Drug Administration
[2] DNDP=Division of Neuropharmacological Drug Products, Food and Drug Administration

treated subject, and 3 diagnosed prior to treatment initiation. Essentially all (19 out of the 20 total[3]) melanomas in the rasagiline-treated subjects occurred in the North American studies TEMPO (monotherapy) and PRESTO (adjunctive therapy). A table summarizing the characteristics of the melanoma cases is contained in Attachment 12.2 of this review.

Because the majority of these melanomas were diagnosed in extension trials without concurrent placebo controls, the DNDP utilized external comparator groups (including population-based cancer registries, melanoma screening programs, and other Parkinson's disease development programs) to ascertain whether more melanomas had occurred in the development program than would be expected. Based on the results of these comparisons, the DNDP reviewers concluded that the overall data supported concerns that rasagiline exposure may be associated with a risk of melanoma.

For the ongoing assessment of this issue, the DNDP Safety Team requested the following additional items from the sponsor:

- An expanded dose-response assessment
- Presentation of data from a sponsor-conducted, North American cohort study in a manner that allows the DNDP to compare it with data from the American Academy of Dermatology (AAD) melanoma screening program.
- Given that the majority of melanoma data was collected from development program studies without concurrent placebo-control, the DNDP also requested that Teva conduct a large simple trial post-approval to better assess the effect of rasagiline exposure on melanoma incidence.

3. ***Inadequate ECG Analysis***: ECG analysis in the *monotherapy* study TEMPO was limited to classification of ECGs into "normal" and "abnormal" categories. The FDA requested that Teva conduct a more thorough analysis (including measurement of ECG intervals and presentation of mean change from baseline and outlier analyses), similar to that performed for the rasagiline adjunctive therapy studies PRESTO and LARGO.
4. ***Additional Analysis of Flu Syndrome***: Flu syndrome and musculoskeletal complaints were commonly reported with rasagiline treatment. The DNDP asked that the sponsor investigate these adverse events further.
5. ***Laboratory and Vital Sign Data***: The sponsor was asked to present these data as change from baseline to *Maximal* Observed Values, as opposed to *Last* Observed Value (LOV) as was done in the original NDA.
6. ***Incomplete Attribution of Adverse Events:*** Within the original NDA submission, approximately 7% of discontinuations due to adverse events (AEs) were not

[3] One subject was diagnosed in TVP-1012/113, an open label extension of a double-blind, randomized, placebo-controlled trial (TVP-1012/112) in levodopa-treated PD patients receiving 0.5 mg rasagiline, 1.0 mg rasagiline or placebo for 12 weeks. These studies were conducted in Hungary and Israel.

attributed to a specific AE. The sponsor was asked to identify the AEs resulting in these study discontinuations.

7. ***Postmarketing Rhabdomyolysis Surveillance:*** Although the DNDP did not consider the two confounded cases of rhabdomyolysis within the rasagiline development program to constitute a significant safety signal, Teva was asked to be vigilant in its postmarketing surveillance. Teva was specifically requested to monitor and submit 15-day postmarketing reports for rhabdomyolysis and related adverse events.
8. ***Issues raised in labeling not specifically referenced in the approvable letter:*** Language was added to the Warning statement entitled "Coadministration of Antidepressants" to be consistent with the language used in the selegiline labeling.

This review evaluates the safety data submitted by Teva in response to the requests in the rasagiline Approvable Letter, with the exception of tyramine-related data, which is addressed in a separate report by DNDP reviewer Dr. Len Kapcala. Emphasis in this review is placed on the continuing assessment of the occurrence of melanoma in association with rasagiline exposure. The sponsor was also asked to provide a summary of the worldwide regulatory actions for rasagiline during the time period since the Approvable Action Letter.

In addition to the data requests above, this review also addresses the most recent sponsor safety update from ongoing trials within the rasagiline development program, with particular attention to deaths, serious adverse events and premature discontinuations due to adverse events.

1.3 Product Information

Rasagiline (1H-Inden-1-amine, 2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate) is an orally-administered, irreversible monoamine oxidase inhibitor (MAOI), reported by the sponsor to be selective for the B form of the enzyme. Preclinical studies suggest rasagiline may elevate extracellular striatal dopamine levels[4]. The sponsor, Teva Neurosciences, is seeking approval for rasagiline within the United States for the treatment of Parkinson's disease. Another MAO-B inhibitor, selegiline, has been approved for treatment of Parkinson's disease in the United States since 1989.

1.4 Worldwide Rasagiline Regulatory Action

1.4.1 Overview

In addition to receiving an Approvable Action Letter from the United States FDA, the sponsor has reported the following worldwide regulatory actions and decisions for rasagiline[5]:

[4] NDA Nonclinical Overview, 2.4.2.1
[5] This section contains a listing of regulatory actions based upon a summaries submitted by Teva, received February 4, 2005 and January 11, 2005 (via e-mail).

Marketing Authorization Granted:

- **European Union (EMEA[6]):** Teva reported[7] that in February 2005 the Committee for Medicinal Products for Human Use (CHMP) approved rasagiline within the European Union, granting marketing authorization for the 1 mg tablet as a monotherapy or adjunctive therapy in Parkinson's disease patients with end of dose symptom fluctuations. The sponsor also provided relevant safety enquiries from the EMEA, as summarized in Section 1.4.5 below.
- **Israel**: Teva reported that in January 2005 the Israeli Ministry of Health issued marketing authorization for rasagiline for the treatment of Parkinson's disease, as both an initial monotherapy in patients with early disease and as adjunctive treatment in moderate-to-advanced disease.

The sponsor stated that rasagiline review is ongoing in — — and provided the equivalent of the FDA's action letters from these regulatory agencies. These are summarized in the subsections below. Review was also reported to be ongoing in — although the sponsor did not submit documents from the — regulatory agency.

1.4.2 — Safety Review

Teva submitted a portion (the "Summary of Safety") of the rasagiline response from the — regulatory agency. The — reviewer noted continuing concern regarding the markedly different adverse event reporting rates between the North American study PRESTO (90%) and European, Argentinean and Israeli study LARGO (50%). The reviewer questioned whether the rates were higher uniformly higher in LARGO compared to PRESTO, or whether the rates were particularly elevated for a subset of adverse events.[8]

Regarding melanoma, the — summary stated "epidemiologic analysis does not support a direct causal relationship between the use of rasagiline and increased rates of melanoma in the study population."

1.4. — Safety Review

The — regulators (— for rasagiline[9], which emphasized their concern regarding the number of melanomas diagnosed during the development program. Specifically, the — reviewers noted

[6] EMEA=European Medicines Agency
[7] E-mail communication received March 3, 2005.
[8] This issue is discussed in Section 4.3 of the FDA rasagiline NDA safety review.
[9] The ' — was submitted by the sponsor as part of their summary of regulatory action worldwide, but had also been submitted (February 1, 2005) through communication between — and the FDA.

an elevated relative risk of melanoma in the rasagiline development program population as compared to a variety of reference groups (including population-based cancer registries such as SEER[10]). In addition, the — reviewers gave consideration to Teva's alternative explanations for the relatively high number of melanomas in the North American studies, although they subsequently noted why they were unconvinced by these assertions. The sponsor's alternative explanations included confounding factors such as other established melanoma risk factors, the implementation of active melanoma screening during the development program, potential shortcomings of the comparator groups, the possibility that melanoma may be associated with Parkinson's disease itself or its other treatments, and a latency period between rasagiline exposure and melanoma diagnosis which was purported to be implausibly short. The — reviewers noted that two *invasive* melanomas diagnosed during the development program occurred in spite of ongoing active melanoma screening.

Reviewer comment: *Further discussion of the occurrence of invasive melanoma, despite all subjects undergoing melanoma screening examinations every three months, is contained in Section 2.5 of this review.*

Taken in conjunction with their efficacy review, the — reviewers concluded that the "lack of unique benefit or substantial advantage of rasagiline over currently available therapies... precludes a positive risk/benefit assessment of rasagiline at this time." The — reviewers also described potential pathogenic mechanisms in which rasagiline could act as a carcinogen, and specified that "substantial, direct evidence which explicitly refutes the involvement of rasagiline in melanoma initiation, promotion and/or progression is required to be submitted to enable reconsideration of this issue."

1.4.4 — Safety Review

Teva forwarded several requests for additional safety data, along with their respective responses, made by the — regulatory agency. For melanoma, the — reviewers noted an increased incidence of melanoma during the rasagiline development program, as compared to the general population, and requested supplementary data from the ongoing, open-label extensions of the three pivotal trials. The — data request stated that "the possibility of a carcinogenic effect of rasagiline with a further increase in the incidence of melanoma should be considered, the longer the treatment period." The sponsor responded to this request with several tables summarizing dose-response data from the various pivotal and extension trials, which are included in Section 2.1 (Dose-Response Analysis) of this review.

With regards to QT interval, the — reviewers stated that "no targeted studies to establish a rasagiline-mediated lengthening of the QT-interval have been carried out." A request was made for a quantitative analysis and discussion of the ECG findings in the

[10] SEER=Surveillance, Epidemiology and End Results Cancer Registry of the United States National Cancer Institute

TEMPO (monotherapy) study (with attention to relationship to dose, especially the 2 mg group), as well as additional Phase I/clinical pharmacology data for both rasagiline and its metabolite, aminoindane. Teva's response to these requests are integrated in the section of this review addressing QT interval (Section 3).

The — reviewers also submitted questions to Teva regarding the tyramine interaction of rasagiline with the typical European (as opposed to American) diet, the abuse potential of rasagiline and possible withdrawal symptoms following rasagiline discontinuation.

1.4.5 European Union Safety Review

As noted above, the European Union granted marketing authorization to rasagiline in February 2005. As part of their review leading to the marketing authorization, the EMEA (European Medicines Agency) made the following safety data request to the sponsor pertaining to the melanoma analysis:

> "The epidemiologic data descriptive and analytic plus the screening data strongly suggested that melanoma is a problem related with the disease and not with rasagiline. Still this should be a topic for special monitoring during the postmarketing pharmacovigilance activities. A proposal for a post-marketing surveillance should be presented. It is in any case likely that the rates of reporting will increase in face of the raised awareness that the publications on this topic are triggering."

Teva responded by stating that a special section dealing with the melanoma issue will be part of all Periodic Safety Reports (PSURs) for rasagiline during postmarketing.

The sponsor also forwarded[11] labeling for rasagiline within the European Union, including the section below pertaining to the occurrence of melanoma:

> 4.4 Special warnings and special precautions for use
>
> "During the clinical development programme the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggest that Parkinson's disease, not any drug in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious lesion should be evaluated by a specialist."

Reviewer comment: *As detailed above, other regulatory agencies have reached a variety of conclusions regarding the occurrence of melanoma during the rasagiline development program, ranging from the opinion that the data are inconsistent with a causal relationship (—) to requiring further preclinical studies demonstrating a lack of*

[11] Forwarded by Teva via e-mail, received February 4, 2005.

carcinogenicity before further consideration of safety in humans could proceed

DNDP proposed labeling regarding safety issues (Contraindications, Warnings and Precautions) including melanoma from the Approvable Letter is provided in Attachment 12.1 of this review.

2. MELANOMA

2.1 Dose-Response Analysis

2.1.1 FDA Request in Approvable Letter

> "The dose-response relationship for melanoma was not well described in the NDA submission. Please present a dose-response analysis for melanoma occurring in association with rasagiline treatment. The denominator should be in person-year units and should reflect time contributed by patients to each dose received (e.g., if a patient was treated with 0.5 mg initially and then later increased to 1 mg, the time they were treated with each dose should be allotted to that dose.)" (NDA 21-641, Rasagiline Approvable Letter, pg. 4)

2.1.2 Sponsor Response

In describing their calculations, the sponsor provided a table (Table 1) below listing the total[12] melanoma cases, the dose at time of diagnosis, and the doses the patient was exposed to before the melanoma was diagnosed. Teva stated that the data used in the dose-response analysis reflected the most recent database lock performed on February 15, 2004 (Response to Approvable Letter: Melanoma, pg. 1).

FDA Table 1: Listing of Subjects Diagnosed with Melanoma and Exposure by Dose at Time of Diagnosis (Adapted from Sponsor Table 1, Response to Approvable Letter: Melanoma, pg. 3)

[12] As noted by the sponsor, the most recent total melanoma count in the rasagiline development program is 24 (See Attachment 12.2 of this review), and not the 21 total melanomas at the time the dose-response calculations were performed.

Table 1. TVP-1012 – Listing of Cases Diagnosed with Melanoma and Exposure by Dose at Time of Diagnosis

	Patient No.	Study	Melanoma Type	Diagnosed on dose	Exposure before MM Diagnosis
1.	164	232	Invasive	2 mg	0.167 yrs.
2.	113	232	In situ	2 mg	1 yr.
3.	246	233	In situ	2 mg	1.55 yrs.
4.	9	233	Invasive	1 mg	2 mg – 1.29 yrs.
					1 mg – 1.31yrs. (2 intervals)
5.	64	233	In situ	1 mg	2 mg – 1.3 yrs.
					1 mg – 1.58 yrs. (2 intervals)
6.			Invasive	1 mg	2 mg – 1.3 yrs.
					1 mg – 3.22 yrs. (2 intervals)
7.	36	233	In situ	1 mg	2 mg – 2.7 yrs.
					1 mg – 0.68 yrs.
8.	209	133	Invasive	0.5 mg	0.45 yrs.
9.	520	135	In situ	1 mg	0.92 yrs.
10.	494	135	In situ	1 mg	0.34 yrs.
11.	116	233	In situ	1 mg	2 mg – 0.94 yrs.
					1 mg – 2.58 yrs. (2 intervals)
12.	613	133	In situ	1 mg	0.54 yrs.
13.	424	135	Invasive	1 mg	0.6 yrs.
14.	169	133	In situ	1 mg	0.5 yrs.
15.	544	233	Invasive	1 mg	2 mg – 1.53 yrs.
					1 mg – 2.17 yrs.
16.	271	135	Invasive	0.5 mg	1.27 yrs.
17.	118	233	Invasive	1 mg	2 mg – 1.49 yrs.
					1 mg – 3.03 yrs.
18.	41604	122	In situ	Placebo	0.35 yrs.
19.	16431	122	Invasive	Before treatment initiation	0
20.	141611	122	In situ	Before treatment initiation	0
21.	756	133	In situ	Before treatment initiation	0

Study Numbers: 232 = North American Monotherapy Study TEMPO; 233 = Open-Label Extension of Monotherapy Study TEMPO; 133 = North American Adjunctive Therapy Study PRESTO; 135 = Open-Label Extension of Adjunctive Study PRESTO.

At the time the sponsor performed these calculations, the number of melanomas (21 cases among 20 patients) was similar to that seen at the time of the original NDA review (20 cases among 19 patients). Teva noted, however, that two additional melanomas were diagnosed after database lock for their calculations, and were not included due to incomplete CRF data at the time of their report preparation. Information on these additional two cases (as well as a third case in one of the two subjects [233 #72/Melanoma in situ, 113 #1012/Two melanomas in situ]), are summarized in the

complete listing of melanomas within the rasagiline development program to date, contained within Attachment 12.2 of this review. All three were treatment emergent cases in subjects receiving rasagiline 1 mg/day.

Reviewer comment: *Although calculation of the dose-response relationship using the total melanomas known would be preferable, presuming that the data for both the cases (numerator) and person-time exposures per dose (denominator) were taken from the same time period before the datalock, the subsequent dose-response analysis should still be valid.*

The sponsor prepared a table (Table 2 below) summarizing the distribution of exposure in the rasagiline clinical trial, presented in patient-years, by dose and study protocol. Teva clarified that the category of exposure to 0 mg was composed of all patients not exposed to rasagiline, namely placebo- and entacapone-treated subjects (Response to Approvable Letter: Melanoma, pg. 4).

Reviewer comment: *As discussed further below, the "0 mg" exposure category actually included one placebo subject and three subjects in which the melanoma was diagnosed prior to treatment initiation.*

FDA Table 2: Distribution of Patients and Exposure by Study and Dose (Adapted from Sponsor Table 2, Response to Approvable Letter: Melanoma, pg. 4)

Table 2. TVP-1012 - Distribution of Patients and Exposure (yrs) by Study and Dose

	Total Exposure (Years)															
	0 mg*		0.5 mg		1 mg		2 mg		4 mg		5 mg		10 mg		All	
	N	YRS	N	YRS	N	YRS	N	YRS	N	YRS	N	YRS	N	YRS	N	YRS
Protocol Name TVP-1012/111	3	0.4	.	.	2	0.3	.	.	.	.	.	.	5	0.6	10	1.3
TVP-1012/112+113	13	2.9	9	2.0	36	98.2	18	30.1	.	.	.	.	.	.	70	133.2
TVP-1012/121	1	0.2	.	.	1	0.2	3	0.5	.	.	.	.	.	.	5	0.8
TVP-1012/122+123+124	456	273.4	.	.	396	318.2	.	.	.	.	.	.	.	.	687	591.6
TVP-1012/132	6	1.2	.	.	7	1.3	7	1.3	.	.	.	.	.	.	20	3.7
TVP-1012/133+135+135A	159	73.8	229	293.4	207	256.2	.	.	.	.	.	.	.	.	472	623.4
TVP-1012/231	13	2.5	.	.	15	2.8	14	2.7	14	2.7	.	.	.	.	56	10.7
TVP-1012/232+232ACT+233	138	63.4	.	.	300	849.0	364	503.2	.	.	.	.	.	.	405	1415.5
TVP-1012/311	13	1.6	.	.	11	1.8	12	1.5	11	1.5	.	.	.	.	47	6.4
TVP-1012/421	.	.	.	.	.	.	19	1.5	.	.	.	.	.	.	19	1.5
TVP-1012/426	.	.	.	.	.	.	13	0.5	.	.	.	.	.	.	13	0.5
TVP-1012/CC547	4	0.0	.	.	6	0.0	4	0.0	.	.	.	.	.	.	14	0.0
TVP-1012/CD596	6	0.2	.	.	.	.	6	0.2	.	.	6	0.2	6	0.2	24	0.7
TVP-1012/P94159	11	1.0	.	.	6	0.6	6	0.6	.	.	.	.	.	.	23	2.2
All	823	420.5	238	295.4	987	1528.5	466	542.0	25	4.2	6	0.2	11	0.7	1865	2791.4

* Placebo and Entacapone treated patients

Reviewer comment: *In the FDA Approvable Letter, the sponsor was requested to distribute person-time in the denominator among the various doses the subject was exposed to (e.g., if a patient was treated with 0.5 mg initially and then later increased to 1 mg, the time they were treated with each dose should be allotted to that dose). As*

assessed by the number of subjects within the treatment groups of the pivotal studies, the sponsor has complied with this request. For example, in the study TEMPO and its extensions (TVP-1012/232 +233), the number of subjects initially randomized to the three treatment groups was 138 subjects (placebo), 134 subjects (rasagiline 1 mg) and 132 subjects (rasagiline 2 mg/day). However, the number of subjects in the rasagiline 1 and 2 mg dose groups in the exposure table contain a considerably higher number of subjects (300 for rasagiline 1 mg and 364 for rasagiline 2 mg), indicating that placebo subjects who transitioned to rasagiline treatment during the open-label extension phase also contributed exposure time to these categories.

Teva stated that in their calculations (numerator), the dose to which the patient was exposed for "the majority of the time" (the modal dose) was used as the "patient's dose" and the melanoma case was attributed to this dose level.

Reviewer comment: *Although assigning the melanoma to the dose the subject was exposed to for the greatest period of time may be an oversimplification of dose exposure, it appears to be the most appropriate method of distributing the numerator cases among dose groups.*

The sponsor's calculations of the melanoma rate per 100,000 patient-years exposure for both invasive and in situ melanoma cases are presented in Table 3 below (Response to Action Letter, Melanoma, pg. 4).

FDA Table 3: Distribution of Melanomas and Rates per 100,000 Patient-Years by Dose (Adapted from Sponsor Table 3, Response to Action Letter: Melanoma, pg. 5)

Table 3. Distribution of MM cases and rates per 100,000 patient-years by dose

	0 mg*	0.5 mg	1 mg	2 mg	All
Number of Invasive MM	1 (238)	2 (677)	5 (327.1)	1 (185)	9 (322)
Number of In situ MM	3 (713)		6 (393)	3 (554)	12 (430)

The numbers in parenthesis are the rates of MM per 100,000 years of exposure

* Includes patients that were diagnosed with melanoma either before treatment initiation or on placebo and were not exposed to rasagiline at the time of diagnosis.

From the above table, the sponsor concluded that there was no increase in the melanoma rate as dose increases, demonstrating that no clear dose-response relationship is present.

Reviewer comment: *In the above dose-response analysis, the sponsor has included cases that were diagnosed before treatment initiation in the "0 mg" dose category. As the purpose of the dose-response analysis is to examine treatment- emergent cases, it is inappropriate to include cases identified prior to treatment initiation. Of the four "0 mg" cases, three were identified prior to treatment (LARGO #16431 [Invasive], LARGO #141611[In Situ], PRESTO #756 [In Situ]; and only one was treatment-emergent, occurring in a placebo-treated subject (LARGO #41604 [In Situ]). When the three melanomas diagnosed prior to treatment are removed, a potential dose-response*

relationship is apparent among total melanomas and to a lesser extent in situ melanomas (See Table 4 below).

FDA Table 4: Dose-Response Calculation for Melanomas within the Rasagiline Development Program, With Cases Assigned to the Modal Dose

	Number of Cases (Cases Per 100,000 PYs)				
	0 mg	**0.5 mg**	**1 mg**	**2 mg**	**All**
Number of Invasive MM	0 (NA)	2 (677)	5 (327)	1 (185)	8 (287)
Number of In Situ MM	1 (238)	0 (NA)	6 (393)	3 (554)	10 (358)
Total Malignant Melanomas (MM)	1 (238)	2 (677)	11 (720)	4 (738)	18 (645)

The numbers in parenthesis are the rates of MM per 100,000 person-years exposure.
*The three cases diagnosed prior to treatment were excluded from this table.

The dose-response relationship above has been calculated with cases assigned to the modal dose (the dose to which the patient was exposed for the longest period of time). Another approach to attributing melanoma cases to a particular dose is to assign cases to the highest rasagiline dose the subject was treated with. A dose response calculation with melanoma cases credited to the highest dose the subject had received is presented in the following table.

FDA Table 5: Dose-Response Calculation for Melanomas within the Rasagiline Development Program, With Cases Assigned to the Subjects' Highest Dose

	Number of Cases (Cases Per 100,000 PYs)				
	0 mg	**0.5 mg**	**1 mg**	**2 mg**	**All**
Number of Invasive MM	0 (NA)	2 (677)	1 (65)	5 (327)	8 (827)
Number of In Situ MM	1 (238)	0 (NA)	4 (262)	5 (922)	10 (358)
Total Malignant Melanomas (MM)	1 (238)	2 (677)	5 (327)	10 (1,845)	18 (645)

Reviewer comment: *In using the highest dose the subject ever received as the dose to which melanomas were assigned (as opposed to modal dose), six melanomas changed from the 1 mg group to the 2 mg group. Using this method of melanoma case assignment (highest treatment dose), increasing dose does not demonstrate a pattern of increasing melanoma occurrence.*

A third approach to attributing cases to a dose is to assign each case to the dose the patient was receiving at the time of diagnosis, as presented in the table below.

FDA Table 6: Dose-Response Calculation for Melanomas within the Rasagiline Development Program, with Cases Assigned to Dose at Time of Diagnosis

	Number of Cases (Cases Per 100,000 PYs)				
	0 mg	**0.5 mg**	**1 mg**	**2 mg**	**All**
Number of Invasive MM	0 (NA)	2 (677)	5 (327)	1 (185)	8 (287)
Number of In Situ MM	1 (238)	0 (NA)	*7 (458)*	*2 (369)*	10 (358)
Total Malignant Melanomas (MM)	1 (238)	2 (677)	*12 (785)*	*3 (554)*	18 (645)

The numbers in parenthesis are the rates of MM per 100,000 person-years exposure.

Reviewer comment: *Calculating the dose-response relationship using the dose at time of diagnosis did not vary substantially from the dose-response calculation using the modal dose (the subgroups which varied between the two methods are shown in italics in the table above). However, the changes do diminish somewhat the potential dose-response relationship for in situ and total melanomas, as compared to the calculation utilizing the modal dose.*

I would consider use of the modal dose as the most appropriate approach for the dose-response analysis, however, because for 15 of the 17 treatment-emergent cases[13] the modal dose represents the sole or the large majority of the subject's dose exposure.

Another sponsor analysis of an exposure (time)-response relationship, presented as the number of melanomas per 100 person-years (PYs) for progressive time periods of rasagiline exposure, is discussed in Section 2.3.6 of this review.

2.2 Screened Population Melanoma Comparison: Sponsor North American Cohort EP002 with the American Academy of Dermatology (AAD) Screening Program

2.2.1 Sponsor North American Cohort Study EP002

2.2.1.1 Cohort Study Methods

Teva conducted two cohort studies of Parkinson's disease (PD) patients not exposed to rasagiline, for the stated purpose of assessing the background frequency and characteristics of skin cancers in the PD patient population. As per the sponsor's discussion, another objective of the study was to ascertain the effect of active dermatologic screening on melanoma prevalence, in comparison to the melanoma prevalence among the unscreened, general population (ISS Appendix 18.3, Section 7.3.1).

Subjects in these two cohort studies consisted of Parkinson's disease patients at various stages of the disease treated with any anti-Parkinson's therapy except rasagiline. One of the cohorts (Sponsor Study EP001) was drawn from nine Israeli medical centers, and the

[13] The two subjects for whom the modal dose did *not* represent the only or the large majority of the patient's exposure were TVP-1012/233 #9 (1 mg: 1.31 years, 2 mg: 1.29 years) and TVP-1012/233 #64 (1 mg: 1.58 years, 2 mg. 1.3 years)(FDA Table 1, pg. 12).

other (Sponsor Study EP002) was assembled from 31 North American medical centers, some of which also provided participants for the rasagiline pivotal studies (ISS Appendix 18.3, Section 7.3.1). The sponsor stated that the participating study sites were instructed to offer participation in the study to all diagnosed PD patients (not previously exposed to rasagiline) who came to the clinics or were known by the physicians working at the clinics (EP002 Final Study Report, 120 Day Safety Update, pg. 18).

Reviewer comment: *The number of melanomas detected in this study may have been influenced by selection bias. It is reasonable to speculate that potential participants would be more likely to volunteer for a study offering screening for melanoma if they believed themselves to be at risk for melanoma, particularly through having a past history of the disease or other skin cancers or precancerous lesions. If so, this could have enriched the cohort with patients prone to melanomas, leading to an elevation in the incidence of melanoma compared to SEER[14] beyond that contributed by active screening or a population of Parkinson's disease patients. There is some precedent for this hypothesis, as another study offering melanoma screening to participants (the American Academy of Dermatology Screening program) also noted that its subjects were at higher risk for melanoma than the general population (For example, whereas an estimated 1% of the United States general population reports a family history of melanoma, 14% of AAD participants did so.)*

This selection bias would presumably have been much less of a factor in the rasagiline pivotal studies, in which melanoma screening was not part of the study protocol at the time most subjects enrolled.

Study participation for subjects in either of the cohort studies was similar, and consisted of two separate visits: one to a neurologist and another to a dermatologist. The neurologist was responsible for recruiting patients with an established diagnosis of PD, obtaining informed consent, recording demographic information, obtaining a medical history, and recording concomitant medications. During the visit to the dermatologist, the subjects reported their past dermatological history and risk factors for melanoma, and underwent a complete dermatological examination with biopsy of any suspected cancerous lesions. Teva stated that slides of all biopsy specimens were evaluated by a central dermatopathologist (EP002 Final Study Report Synopsis, 120 Day Safety Update).

A more detailed description of this study (adapted from the sponsor's synopsis in the final study report) is provided in Attachment 12.3 of this review.

Teva noted a difference between the method of calculation of the melanoma incidence rates in the pivotal studies for rasagiline development program as compared to the EP001/EP002 cohorts. The incidence rate of melanoma in the development program was

[14] Surveillance, Epidemiology and End Results (SEER) Cancer Registry of the United States National Cancer Institute (NCI)

determined prospectively, while in the cohort studies the incidence rate of melanoma was determined retrospectively by *combining* the total number of melanoma cases diagnosed in the two years *prior* to the study with the melanomas diagnosed by screening during the study (EP002 Final Study Report Synopsis, 120 Day Safety Update).

Reviewer comment: *Based upon the description provided by the sponsor, the EP001/EP002 study designs seem to be an intermediate design between a cross-sectional study (due to the one-time dermatologic screening) and a retrospective cohort study (due to the collection of the subject's prior melanoma history), rather than strictly a cohort study. Because the sponsor has asserted that the EP001/EP002 cohort studies provide support for the hypothesis that the number of melanomas within the rasagiline development program was attributable to the institution of a screening program, the comparison of melanoma incidence in these cohorts to the AAD melanoma incidence will include only those melanomas diagnosed during the dermatologic screening component (i.e. melanomas from the subjects prior medical history will be excluded.) In addition, the majority of participants in the AAD study underwent a single dermatologic screening (~80%), so restricting the comparison to melanomas diagnosed only through dermatologic screening in the sponsor cohort study would result in a more appropriate comparison. Finally, the reporting of melanomas diagnosed over the prior two years in the EP001/EP002 cohorts would be prone to recall bias, and hence not very reliable (medical record verification was not routinely performed to validate patient report).*

2.2.1.2 EP002 Results

Melanomas Identified Through Dermatologic Screening

In the North American Cohort EP002, Teva reported that a total of 2,106 patients underwent dermatologic examination. Of these, 24.6% were found to have suspicious lesions, and 16.4% had suspicious pigmented lesions. Biopsies were performed on 656 lesions from 393 patients. Teva reported that these biopsies identified 24 melanomas (20 in situ and 4 invasive), representing 1.1% of the total study population (0.9% for in situ and 0.2% for invasive) (EP002 Final Study Report Synopsis, 120 Day Safety Update).

Melanomas from Subjects' Prior History

Seventy three (73) cohort members had reported a history of melanoma (39 in situ, 12 invasive and 12 unknown), four of whom had an additional melanoma diagnosed during the study screening (EP002 Final Study Report Synopsis, 120 Day Safety Update).

Reviewer comment: *The study protocol did not state whether medical records were obtained for subjects reporting melanomas, but instead indicated that "a qualified dermatologist at the investigative site will record the dermatologic history" (120 Day Safety Update, Clinical Study Survey, pg. 6). The sponsor was asked to clarify whether*

medical records were sought. Teva's response[15] did not address the specific protocol for medical records verification, but did state that 21 of a total of 74[16] reported past melanomas were corroborated by medical records. The lack of medical record verification in the remaining 53 cases could introduce a significant source of error if subjects incorrectly self-reported a history of melanoma when they had in fact experienced another, more common form of skin cancer, such as basal or squamous cell carcinoma.

Total Melanomas from Both Dermatologic Screening and Prior History

Teva reported that a total of 97 melanoma cases were recorded in *either* the patient's medical history *or* diagnosed by the dermatological examinations during the EP002 cohort study. These included 26 cases of invasive melanoma, 59 cases of melanoma in-situ cases, and 12 cases of unclassified melanoma (EP002 Final Study Report Synopsis, 120 Day Safety Update).

Sponsor Comparison of Cohort Study Results to SEER

The sponsor reported that the total prevalence of melanoma from the dermatologic screening examinations in the cohort study was 1.1%, which Teva stated was 18.3 times higher than that reported in SEER[17] registries for the United States during 1999. Teva also reported, however, that a ratio of observed to expected melanomas indicated that the incidence of melanoma for this cohort study was 6.9 times higher than in a comparable age and sex matched population in SEER (EP002 Final Study Report Synopsis, 120 Day Safety Update).

Reviewer comment: *Although the EP002 study report stated that the first subject in the study was enrolled in January 13, 2003 and the last in September 7, 2003, SEER reference data from 1999 was utilized for comparison. The most recent data available in SEER at the time of this report writing (March 2005) was for 2001. In any case, the sponsor's statement that the prevalence in the cohort study population was 18.3 times higher than in the United States does not appear to be adjusted for age and gender, and is therefore of limited utility: the sponsor subsequently stated that the age and gender matched comparison demonstrated an observed to expected ratio of 6.9 for cohort data compared to SEER. If one presumes that the SEER rates for melanoma are higher in 2001 than in 1999 (not unreasonable, given the increasing risk of melanoma in the general population over time), the observed to expected ratio would be less marked than the 6.9 fold increase calculated by Teva.*

[15] Sponsor response to FDA reviewer question, received via e-mail on April 18, 2005.
[16] Teva stated that a total of 74 (instead of 73) retrospective melanomas was used in this context because one additional subject with a past melanoma that "could not be supported by diagnosis date" was excluded from the final analysis.
[17] SEER = Surveillance, Epidemiology and End Results Cancer Registry of the United States National Cancer Institute (NCI)

An additional limitation of the comparison of the cohort study data with SEER is that because the two populations differ with regard to both the presence of active melanoma screening and Parkinson's disease prevalence, it is not possible to distinguish how these factors may individually contribute to differences in the melanoma rates between the two populations.

Sponsor Conclusions

Teva reported that the prevalence ratio of invasive to in situ melanoma, as identified by the dermatologic screening within the study, was 1:5 (4 invasive melanomas: 20 in situ melanomas). The sponsor asserted that this finding suggests that proactive screening, as conducted in this cohort study and in the rasagiline clinical trials, is prone to identify a higher numbers of in situ melanoma cases due to the elimination of the "lead-time detection bias" during which in situ cases progress to invasive melanoma (EP002 Final Study Report Synopsis, 120 Day Safety Update).

From this study, and the methodologically similar study cohort EP001[18] in Israel, the sponsor concluded that proactive dermatological screening, as also performed in some of the rasagiline pivotal studies, is associated with an increased incidence of melanoma identification. The sponsor suggested that the studies may also demonstrate an increased risk of melanoma among PD patients (EP002 Final Study Report Synopsis, 120 Day Safety Update).

2.2.2 FDA Request in Approvable Letter

> "You have provided some evidence that melanoma is more common in patients with Parkinson's disease. We would like to perform an analysis comparing two populations, both subject to active surveillance for melanoma: the American Academy of Dermatology cohort and the cohort of North American Parkinson's disease patients that you studied. We have the data for the AAD cohort broken down by age and gender; we ask that you submit the incidence of melanoma from the North American cohort study EP002 broken down by the following age categories (<45, 45-54, 55-64, 65-74, 75+, for invasive and in situ tumors separately) and gender. Our Safety Group will perform the analyses." (NDA 21-641, Rasagiline Approvable Letter, pg. 5)

2.2.3 Sponsor Response

[18] I have not included in depth discussion of the EP001 results because the incidence of melanoma in Israeli Parkinson's disease patients is less relevant to the expected effect of rasagiline in the US population on melanoma incidence (because of the substantial difference in risk factors for melanoma including degree of sun exposure and prevalence of fair-skinned complexion).

Teva submitted the following table summarizing data from their North American cohort study EP002 divided as per the request above to facilitate comparison with the American Academy of Dermatology (AAD) data.

FDA Table 7: Distribution of Melanoma Cases within the Sponsor's North American Cohort Study EP002 (Adapted from Sponsor Table 4, Response to Action Letter: Melanoma, pg. 6).

Table 4. Distribution of MM cases by Sex and Age Category

Age (Years)	Invasive MM			MM In situ		
	Female	Male	All	Female	Male	All
Age<45	0	0	0	0	1	1
45<=Age<55	0	0	0	0	0	0
55<=Age<65	0	1	1	2	2	4
65<=Age<75	0	0	0	2	5	7
75<=Age	0	3	3	2	6	8
All	0	4	4	6	14	20

As the above table did not contain the denominator information needed to perform the rate calculations, the sponsor subsequently submitted the following table:

FDA Table 8: Number of Subjects in Sponsor North American Cohort Study EP002 Per Age Strata (Adapted from Sponsor Response to FDA Questions: Revised Table 4 from North American Study EP002. Submitted via EDR, Received February 4, 2005)

Age Category (Years)	Number of patients per age category		
	Female	Male	All
Age<45	10	28	38
45<=Age<55	61	128	189
55<=Age<65	161	335	496
65<=Age<75	236	511	747
75<=Age	201	435	636
All	669	1437	2106

2.2.4 DNDP Comparison of Sponsor Cohort Study Data to the AAD Screening Program

2.2.4.1 Comparison Background

As noted in the FDA request within the Approvable Letter, the sponsor has maintained that the relative increase in melanomas in rasagiline-treated subjects within the development program is largely attributable to, or at least confounded by, the fact that these subjects are Parkinson's disease patients, with unique melanoma risk factors in the form of both the disease itself and its therapies. In order to test this hypothesis, the sponsor initiated two cohort studies of melanomas within PD patients *not* exposed to rasagiline. As noted in the Section 2.2.1.1 above, one of studies was conducted in Israel, and the other in North American. Because geographic location can strongly influence melanoma rates, the DNDP requested data from the sponsor North American cohort study only. This refines the comparison, as both the sponsor EP002 cohort study data and the American Academy of Dermatology screening program data were collected from North American populations undergoing active surveillance for melanoma, although the difference in Parkinson's disease status between the two populations remains. (An overview of the AAD Skin Cancer Screening Program is provided in Attachment 12.4 of this review.)

Another difference between the two study populations was the time period during which the screening was performed. The rates requested from the AAD represent screenings performed from 1992 to 1994[19]. Subjects in study EP002 were enrolled between January 2003 and September 2003, and so underwent screening approximately ten years later than the AAD cohort. In the same time period (1993 to 2003), the rate (United States age-adjusted rate for all races)[20] of melanomas in SEER[21] increased from 14.5 per 100,000 (1993) to 18.7 per 100,000 (2001)[22]. There could therefore be an approximately 28% increase in the number of melanomas in the EP002 cohort compared to the AAD data based on the year of screening alone.

Finally, although both populations were North American, the AAD population was drawn exclusively from the United States, whereas approximately 20% (439/2295, 19.1%) of subjects in study EP002 were from Canadian sites. Given the large effect that latitude has on melanoma rates, the inclusion of these Canadian subjects may be expected to lower the rate of melanomas in study EP002, as compared to a study population composed solely of residents of the United States.

2.2.4.2 Comparison Methods

[19] Although the AAD Skin Cancer Screening program was conduced from 1985 to 2000, extensive follow-up of biopsies from presumptive melanomas was only conducted for the three-year period from 1992 to 1994, as described in more detail in Attachment 12.4 of this review.

[20] http://canques.seer.cancer.gov/cgi-bin/cq_submit?dir=seer2001&db=1&rpt=TAB&sel=1^0^0^49^^^0^0&x=Year%20of%20diagnosis^5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33&y=Race^0,1,2&dec=4&referrer=0

[21] SEER provides summary statistics on invasive melanomas only, but a similar increase in in situ melanomas is presumed.

[22] The most recent data available in SEER at the time this report was written was for 2001.

The structure of the comparison of the sponsor EP002 North American cohort data with the AAD data was similar to the comparison of the rasagiline development program melanoma data with the AAD data in the primary safety review for the original NDA submission[23]. The table with melanoma rates for the AAD population stratified by age and sex is provided in Attachment 12.5 of this review. The following two tables (one for male and one for female subjects) apply the melanoma rates found in the AAD screening program to the population of the sponsor EP002 cohort study (as summarized by the sponsor in Tables 4 and 5 above). The resulting number of expected invasive and in situ melanomas as per the AAD rates will be compared with the observed number of melanomas within the EP002 cohort study in the following section.

FDA Table 9: Calculation of Expected Melanomas for ***Men*** in the Sponsor North American Cohort EP002 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	28	71.6	0.02	28	22.6	0.006
45-54	128	176.2	0.23	128	79.0	0.10
55-64	335	170.4	0.57	335	70.2	0.24
65-74	511	205.5	1.05	511	79.0	0.40
75+	435	167.5	0.73	435	51.5	0.22
Total	1437		**2.6**	1437		**0.97**

FDA Table 10: Calculation of Expected Melanomas for ***Women*** in the Sponsor North American Cohort Study EP002 Using Melanoma Rates from the American Academy of Dermatology Screening Program

Age Group	**Invasive Melanoma**			**In Situ Melanoma**		
	# of Patients*	**AAD Rate per 100,000***	**Expected as per AAD**	**# of Pts.***	**AAD Rate per 100,000***	**Expected as per AAD**
<45	10	58.5	0.006	10	13.7	0.001
45-54	61	72.5	0.04	61	49.6	0.03
55-64	161	71.8	0.12	161	32.3	0.05
65-74	236	80.4	0.19	236	22.5	0.05
75+	201	150.2	0.30	201	40.1	0.08

[23] Comparison of melanoma data between the rasagiline development program and the AAD program is detailed within the original NDA safety review, Section 5.5.3.

Total	669		**0.66**	669		**0.21**

2.2.4.3 Comparison Results

The observed to expected ratios for observed melanomas (by dermatologic screening) in the EP002 cohort compared to the number expected as per the AAD rates applied to the EP002 population are presented in the following table.

FDA Table 11: Observed to Expected Comparison of Melanomas in Sponsor North American Cohort Study EP002, using the AAD Screening Program as a Reference Population

Melanomas	**Number Observed** *	**Number Expected** **	**Obs./ Exp. Ratio**	**95% CI**[24]
Invasive	4	3.3	1.2	0.3,3.1
In Situ	20	1.2	16.7	10.2, 25.7
Total	24	4.5	5.3	3.1, 7.9

* Number of melanomas diagnosed in North American through dermatologic screening
** Number of melanomas expected within rasagiline subjects as per the rates of the screened population within the AAD screening program

2.2.5 Melanoma Comparison from the Original NDA Review: Rasagiline Development Program with the American Academy of Dermatology (AAD) Screening Program

In the evaluation of the initial NDA submission, melanoma data from the rasagiline development program was compared to the AAD data in a manner similar to that for the EP002 comparison described above. Results of this analysis are redisplayed in the table below for the purposes of comparison.

FDA Table 12: Comparison of the Expected rate of Melanoma in the Rasagiline Development using the AAD Screening Program as a Reference Population (Taken from FDA Table 63, pg. 129, NDA Safety Review for Rasagiline, Prepared by M. Lisa Jones MD, MPH, dated July 5, 2004)

Invasive Melanoma	**In Situ Melanoma**

[24] Calculated as 95% Poisson confidence interval based on methods described in: Liddell FD. Simple exact analysis of the standardized mortality ratio. Journal of Epidemiology and Community Health 1984;38:85-88., and Silcocks P. Estimating confidence limits on a standardized mortality ratio when the expected number is not error free. Journal of Epidemiology and Community Health 1994;48:313-317. Performed by Java applet calculator at http://home.clara.net/sisa/smr.htm.

Number Observed *	Number Expected **	Obs./ Exp. Ratio	95% CI ***	Number Observed *	Number Expected **	Obs./ Exp. Ratio	95% CI ***
4	1.52	2.6	0.72, 6.74	6	0.59	10.2	3.7, 22.1

* 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

Reviewer comment: *It is notable that the same pattern of a substantial elevation of in situ but not invasive melanomas was evident in the AAD comparison to both the EP002 screened cohort population and the screened rasagiline development program population. This suggests that the theories regarding the relative prevalence of invasive versus in situ melanomas in the AAD population (discussed in Section 2.2.7 below) may generalize to the use of the AAD program as a comparator across analyses.*

2.2.6 EP002 Melanomas Stratified by Concomitant Levodopa

As there has been general concern[25] of a connection between levodopa treatment and melanoma, the sponsor was asked to provide[26] the following table stratifying melanoma incidence in the EP002 study population by levodopa exposure. EP002 does not lend itself well to the examination of a potential effect of levodopa, however, as the majority of subjects had longstanding Parkinson's disease and had therefore received levodopa treatment[27]; the average duration of PD among subjects was 7.1 years and 92% were treated with some form of levodopa.

FDA Table 13: Incidence of Melanomas Diagnosed During EP002 Dermatology Screening Examinations By Levodopa Treatment (Adapted from Sponsor Table 5, Responses to FDA Reviewer Request, Received Via E-Mail on April 18, 2005)

Levodopa Exposure	**N Subjects (% of Total)**	**N Invasive Melanomas[a] (Percent Subjects)**	**N In Situ Melanomas[a] (Percent Subjects)**	**N Total Melanomas[a] (Percent Subjects)**
With Levodopa Treatment	1783	4 (0.2%)	17 (1%)	21 (1%)
Without Levodopa Treatment	323	0 (NA)	3 (0.9%)	3 (0.9%)

[25] This issue discussed in Section 5.4.3.2.1 of the FDA NDA Safety Review for Rasagiline, Prepared by M. Lisa Jones MD, MPH, dated July 5, 2004.
[26] Table forwarded by electronic mail (received April 18, 2005) in response to a request by this reviewer.
[27] Although the protocol called for both early and late Parkinson's disease patients to be enrolled in EP002, the actual study population was composed primarily of patients with more advanced disease who had received levodopa treatment (92%).

a. Melanomas were limited to those diagnosed during the dermatologic screening examination only (i.e., melanomas retrospectively identified through medical history from the two-years prior to study enrollment were excluded.)

Reviewer comment: *Although the risk of invasive melanomas was minimally higher in subjects receiving levodopa (based on a small number of cases), the risk of both in situ melanomas and total melanomas was similar in subjects who were or were not treated with levodopa. The EP002 data therefore does not support a role for levodopa, although this conclusion is limited by the fact that the study was not designed to address this question.*

2.2.7 FDA Discussion and Conclusions

As shown in FDA Table 11 above, there is a 5.3-fold (95% CI 3.1, 7.9) elevation in the ratio of observed (EP002) to expected (AAD) for total melanomas. This elevation is principally driven by the elevation of in situ melanomas (observed to expected ratio of 16.7 [95% CI 10.2, 25.7] for in situ melanomas, but only 1.2 [95% CI 0.3, 3.1], for invasive melanomas). This large difference in relative elevation between the invasive and in situ melanoma subtypes is somewhat perplexing. In their discussion of the relatively high ratio of in situ to invasive (5:1) melanomas within the EP002 cohort itself, the sponsor suggested that this may be due to "over-screening" detecting a higher number of melanomas before they progressed to the invasive stage. However, in comparing the EP002 observed results to that expected based on rates within the AAD screening program, it is more difficult to explain the elevation of in situ melanomas in the EP002 study, as both populations were screened for melanoma at essentially the same frequency (one time) and were both likely to be at higher risk of melanoma than the general population by virtue of volunteering for a melanoma screening study. In addition, it seems physiologically unlikely that either PD or its treatment (the principle difference between the two populations) would predispose one to in situ, but not invasive, melanomas, as the overwhelming majority of in situ melanomas are expected to progress to invasive melanoma over time.

One explanation for this discrepancy between in situ and invasive melanomas is that although both groups may be at high risk of melanoma (by virtue of the fact that subjects volunteered for screening)[28], the AAD population may be at even greater risk for *invasive* melanomas. The basis for this statement is that the AAD advertised its free screening program in the local media and may therefore have been more likely to recruit subjects without access to regular health care. This is supported by data collected from the AAD screenees: 80% did not have a regular dermatologist, 60% had never had their skin checked by any doctor, and 51% stated they would not have seen a doctor for skin cancer

[28] The high number of melanomas in the retrospective component (the two-years prior to study entry) in EP002 and information on personal and family history of skin cancer collected for AAD screening participants suggest that both study populations were at higher risk for melanoma than the United States population in general.

without the free screening.[29] Subjects in EP002, in contrast, were recruited through their outpatient medical providers and presumably had more consistent access to medical care, making them more likely to have had worrisome skin lesions (and hence melanomas) removed prior to undergoing the study screening. This factor and probable increased vigilance for any subsequent skin cancers in subjects with a past melanoma history may have lowered the relative frequency of invasive compared to in situ melanomas in the EP002 cohort.

A second hypothesis regarding the relative increase of in situ compared to invasive melanomas stems from the method by which melanoma-related medical records were collected within the AAD screening program. As described in Attachment 12.4 of this review, confirmatory medical records were received for only 72% of lesions suspicious for melanomas. Presuming that screenees with invasive melanomas may have been more likely to return medical records than screenees with in situ melanomas (due to the more serious implications of an invasive melanoma), the medical records collection may have been less complete for in situ melanomas. A relative decrease for in situ melanomas in the AAD, which were used to calculate the number of expected melanomas in the observed to expected comparison, could contribute to an elevated observed to expected ratio between the EP002 and the AAD in situ melanomas.

The preceding hypotheses on the discrepancy between in situ and invasive rates, although plausible, cannot be verified. The question is therefore whether the five-fold elevation of *total* melanomas (observed to expected ratio 5.3, 95% CI 3.1, 7.9) is sufficient for reaching conclusions on the role of PD and its treatments on melanoma development. This reviewer believes that the large incongruity in the elevation of melanoma rates by pathological subtype suggests that factors other than the presence of PD and its treatments are influencing either melanoma detection or progression, undermining the conclusions that can be reached from the analysis. At best, the EP002/AAD comparison may suggest a role for PD and its treatment in the development of melanoma. It cannot, however, directly speak to a potential contributory role for rasagiline, as rasagiline treatment was not a part of either study.

For these reasons and others discussed in Section 2.6 below, this reviewer believes that the EP002/AAD comparison and other post-hoc analyses will not substitute for a study designed to directly address a relationship between rasagiline treatment in Parkinson's disease patients and melanoma. The findings of the EP002/AAD comparison, although intriguing, are not sufficient to form the basis of a decision on the safety of rasagiline with respect to melanoma development.

[29] Geller et al. The first 15 years of the American Academy of Dermatology skin cancer screening programs: 1985-1999. J Am Acad Dermatol 2003; 48(1):34-41.

2.3 Delayed Versus Immediate Start Analysis

2.3.1 FDA Request in Approvable Letter

> "We ask that you perform a pooled analysis of all patients randomized in the North American studies, TEMPO and PRESTO. For all patients randomized to rasagiline or placebo we ask that you include all melanomas ascertained in those patients throughout the placebo-controlled phases, the active-controlled phases and even the open-label extensions. We ask that you compare the numbers of melanomas observed throughout all the above 3 phases for the two groups: 1) patients randomized to rasagiline from the start, and 2) patients with a "delayed start" of rasagiline." (NDA 21-641, Rasagiline Approvable Letter, pg. 5)

2.3.2 Summary of the PRESTO and TEMPO Pivotal Trials

As noted in the request to the sponsor in the Approvable Action letter, subjects in the delayed and immediate start analysis were drawn from the North American pivotal studies TEMPO and PRESTO. These studies are summarized below to assist in the interpretation of the delayed and immediate start analysis described below in Section 2.3.3.

1. TEMPO (Rasagiline Monotherapy, Study TVP-1012/232) was a multi-national (Canada and the United States) study of rasagiline monotherapy in early Parkinson's disease (PD) patients. Participants had an average PD duration of one year and the majority had not been previously treated with an anti-Parkinson's disease medication.

The study began with a six-month, placebo-controlled, double-blind phase with three treatment groups: rasagiline 1 mg/day (134 subjects), rasagiline 2 mg/day (132 subjects) and placebo (138 subjects). This was followed by a six-month double-blind active treatment phase. Patients completing the first 26 weeks or whose symptoms required additional anti-PD therapy could proceed to the second (active) phase of double-blind treatment in which all patients received rasagiline, 1 or 2 mg/day. Subjects receiving rasagiline in the placebo-controlled phase remained on their originally assigned dose, and placebo-treated subjects were switched to rasagiline, 2 mg/day. Three hundred eighty (380) patients entered the active treatment phase. During this phase subjects could begin an additional anti-PD therapy (dopamine agonists or levodopa) as per investigator discretion, and 32% (n=123) did so.

Participants subsequently had the option of entering an open-label extension (TVP-1012/233). Three hundred and six persons (306) had entered and 224 were ongoing in the open-label extension at the time of the NDA submission. Initially all extension subjects were assigned to rasagiline 2 mg/day, but this was amended to 1 mg/day approximately 18 months into the extension study, after available data showed no efficacy advantage for the higher dose (Clinical Summary 2.5.4.3.1.3).

As per the study reports, the three phases of TEMPO commenced on the following dates: Placebo-controlled phase (TVP-1012/232): November 1997, Active treatment phase (TVP-1012/232): June 1998, Open-label phase (TVP-1012/233): January 1999.

2. PRESTO (Levodopa Adjunct Study TVP-1012/133) was a multi-center, multinational (Canada and the United States), double-blind, parallel group trial conducted in 472 Parkinson's disease (average duration nine years) patients treated chronically with levodopa (Proposed Labeling, pg. 9).

Patients were randomly assigned to receive placebo (159 patients), rasagiline 0.5 mg/day (164 patients), or rasagiline 1 mg/day (149 patients), and were treated for 26 weeks. This was followed by a 26-week, double-blind active treatment phase (TVP-1012/135) in which rasagiline–treated participants were continued on their previous dosage, and placebo-treated patients were randomized to one of the rasagiline treatment groups. Three hundred thirty eight (338) patients entered the active treatment phase, and 147 were ongoing at the time of the initial NDA submission.

Subjects had the option of entering a subsequent open-label phase, in which all patients received rasagiline 1 mg for 12 months or "until rasagiline is marketed."

As per the study reports, the three phases of PRESTO commenced on the following dates: Placebo-controlled phase (TVP-1012/133): December 2000, Active treatment phase (TVP-1012/135): July 2001, Open-label phase (TVP-1012/135A): ~December 2001.

2.3.3 Sponsor Response

Teva provided the following table listing the 17 melanomas diagnosed among subjects randomized to the TEMPO and PRESTO studies, summarizing the phase in which they were diagnosed and the treatment group to which they belonged. The sponsor stated that one additional melanoma was diagnosed in a PRESTO subject prior to treatment initiation (#756) and was therefore not included. Teva stated that the data reflects the latest database lock, performed on February 15, 2004 (Response to Approvable Letter: Melanoma, pg. 7).

FDA Table 14: North American Studies TEMPO and PRESTO: Melanoma Cases by Pathology, Treatment Group and Study Phase of Diagnosis (Adapted from Sponsor Table 5, Response to Approvable Letter: Melanoma, pg. 7)

	Patient No.	Study	Melanoma Type	Type	Phase in which MM Diagnosed
1.	164	232	Invasive	Randomized to rasagiline	Placebo Controlled
2.	113	232	In situ	Randomized to rasagiline	Active Treatment Phase
3.	246	233	In situ	Randomized to rasagiline	Open Label
4.	9	233	Invasive	Randomized to rasagiline	Open Label
5.	64	233	In situ	Randomized to rasagiline	Open Label
6.			Invasive	Randomized to rasagiline	Open Label
7.	36	233	In situ	Randomized to rasagiline	Open Label
8.	209	133	Invasive	Randomized to rasagiline	Placebo Controlled
9.	520	135	In situ	Randomized to rasagiline	Active Treatment Phase
10.	494	135	In situ	Delayed Start	Active Treatment Phase
11.	116	233	In situ	Randomized to rasagiline	Open Label
12.	613	133	In situ	Randomized to rasagiline	Placebo Controlled
13.	424	135	Invasive	Randomized to rasagiline	Active Treatment Phase
14.	169	133	In situ	Randomized to rasagiline	Placebo Controlled
15.	544	233	Invasive	Randomized to rasagiline	Open Label
16.	271	135A	Invasive	Randomized to rasagiline	Open Label
17.	118	233	Invasive	Delayed Start	Open Label

Reviewer comment: *The relatively small number of melanomas occurring during these studies (from the perspective of epidemiologic comparisons) and the fact that the delayed start group contains only two melanomas could detract from the robustness of the comparison.*

It is noteworthy that the distribution of melanomas in the delayed and immediate start groups is similar for the two studies: TEMPO - 9 immediate start:1 delayed start melanoma, PRESTO – 6 immediate start:1 delayed start. Figures depicting the distribution of cases over time in the individual and combined studies are provided in Attachment 12.6.

Further information on the melanomas occurring in these seventeen subjects is summarized in the table below.

FDA Table 15: Melanoma Characteristics of Subjects in the Delayed and Immediate Start Melanoma Analysis

	Study	Pt. #	Months Rasagiline Prior to Melanoma Diagnosis	Date of Melanoma Diagnosis (Biopsy)	Melanoma Screening at Time of Diagnosis*	Study Phase of Melanoma Diagnosis
"Delayed Start" Melanomas						
1	PRESTO Ext.	494	4 months	[redacted]	1st Derm. Exam	Active Control
2	TEMPO.	118	53 months	[redacted]	6th Derm.	Open-Label

	Ext.				Exam	
"Immediate Start" Melanomas						
3	TEMPO Ext.	164	3 months		Dx'ed Prior to Screening	Placebo-Control
4	PRESTO	209	6 months		1st Derm. Exam	Placebo-Control
5	PRESTO Ext.	613	6 months		2nd Derm. Exam	Placebo-Control
6	PRESTO	169	6 months		3rd Derm. Exam	Placebo-Control
7	PRESTO Ext.	424	7 months		1st Derm. Exam	Active Control
8	PRESTO Ext.	520	9 months		1st Derm. Exam	Active Control
9	TEMPO	113	13 months		Dx'ed Prior to Screening	Active Control
10	PRESTO Ext.	271	14 months		6th Derm. Exam	Open-Label
11	TEMPO Ext.	246	16 months		Dx'ed Prior to Screening	Open-Label
12	TEMPO Ext.	9	31 months		Dx'ed Prior to Screening	Open-Label
13	TEMPO Ext.	64	35 month		Dx'ed Prior to Screening	Open-Label
14	TEMPO Ext.	36	38 months		Dx'ed Prior to Screening	Open-Label
15	TEMPO Ext.	116	42 months		1st Derm. Exam	Open-Label
16	TEMPO Ext.	544	47 months		4th Derm. Exam	Open-Label
17	TEMPO Ext.	64	55 months		2nd Derm. Exam	Open-Label

*Quarterly dermatological screening examinations were initiated between October and December 2001 as a safety measure after the sixth melanoma was identified in the development program. Melanomas categorized as "Dx'ed prior to screening" were treatment emergent and diagnosed through trial follow-up visits before the requirement for quarterly dermatological examinations was initiated.

As shown in the following table, Teva also provided the distribution of melanoma cases with respect to rasagiline exposure (in patient-years) by treatment group and study phase of diagnosis.

FDA Table 16: North American Studies TEMPO and PRESTO: Distribution of Melanomas and Rasagiline Exposure (Patient-Years) by Group and Phase in which Melanoma was Diagnosed (Adapted from Sponsor Table 6, Response to Approvable Letter: Melanoma, pg. 8)

Phase	Delayed Start			Randomized to Rasagiline			All		
	Exposure to Rasagiline	No. of MM Cases Detected		Exposure to Rasagiline	No. of MM Cases Detected		Exposure to Rasagiline	No. of MM Cases Detected	
		Invasive	In situ		Invasive	In situ		Invasive	In situ
Placebo Controlled	0.0	0	0	266.9	2	2	266.9	2	2
Active Treatment Phase	118.8	0	1	240.2	1	2	359.0	1	3
Open Label	438.3	1	0	837.5	4	4	1275.8	5	4
All	557.2	1	1	1344.6	7	8	1901.8	8	9

The sponsor did not provide any further analyses or commentary on the delayed versus immediate start rasagiline exposure.

2.3.4 FDA Analysis

Interpretation of the occurrence of melanomas within the delayed and immediate rasagiline start groups described above is not straightforward. It can be conceptualized and approached in several ways, including the following:

1. ***Standardization to Rasagiline Person-Year Exposure:*** When standardized to cases per 1000 person-years exposure to rasagiline, the rate of total melanomas in the immediate start group (15/1344.6, or 11.6 melanomas per 1000 person-years [95% C.I. 6.2,18.4]) was considerably higher than in the delayed start group (2/557.2 person-years, or 3.6 melanomas per 1000 person-years rasagiline exposure [95% C.I. 0.4,13.0]). As this comparison controls for rasagiline exposure across both groups, the primary factor differing between the two groups is latency from study enrollment from the placebo period in the delayed start group.

FDA Table 17: Melanomas Per 1000 Person-Years (PYs) in the Delayed and Immediate Start Treatment Groups for the North American Studies TEMPO and PRESTO

Treatment Group	Cases Per PYs (Total)	Cases Per 1000 PYs	95% C.I.s[30]
Immediate Start	15 cases/1344.6 PYs	11.6/1000 PYs	6.2, 18.4
Delayed Start	2 cases/557.2 PYs	3.6/1000 PYs	0.4,13.0

Reviewer comment: *Although the immediate start group demonstrated an approximately three-fold relative increase compared to the delayed start group, the confidence intervals between the two groups overlap. The difference in melanoma rates between the two groups may therefore not be as large as the three-fold increase.*

[30] Calculated via java applet, Open Source Statistics for Public Health, http://www.openepi.com/Jan2004/menu/OpenEpiMenu.htm (Two Person Time Rates). Calculated based on method described in Martin DO, Autin H. Exact estimated for a rate ratio. Epidemiology (7) 1996; 29-33.

2. ***Risk During a Fixed Time of Rasagiline Exposure:*** As the primary difference between the two groups is the decreased exposure to rasagiline in the delayed start group by virtue of the initial placebo treatment, the three-fold increase in melanomas in the immediate start group suggests a potential role for duration of rasagiline treatment in the development of melanoma. This hypothesis would be strengthened if the melanomas in the immediate start group primarily occurred later in the observation period, suggesting either the need for a latency period or a threshold of cumulative rasagiline exposure for melanoma development.

   Under the hypothesis that some latency period may be required between rasagiline exposure and melanoma development, an analysis comparing melanoma risk during a set follow-up period of rasagiline exposure for each group was also performed. To simplify the analysis, the number of subjects entering the placebo-controlled phase of the studies was used as the denominator for the risk calculation (PRESTO: 159 Placebo [Delayed Group], 313 Rasagiline; TEMPO: 138 Placebo [Delayed Group], 266 Rasagiline). However, the number of patients is expected to decrease as the study progresses due to subject discontinuation, and the use of this denominator in the later time periods will underestimate the risk to some degree. As a gauge of this underestimation, of the total of 404 TEMPO subjects who entered the placebo-controlled phase, 380 entered the active control phase and 306 entered the open-label phase: a 25% attrition over time. In addition, although the discontinuation rates for overall rasagiline-treated subjects in the two studies were similar (TEMPO: 2%, PRESTO: 7%), within the individual studies the discontinuation rate for rasagiline-treated subjects was higher than that for placebo subjects (TEMPO 0.7%, PRESTO 5%).[31]

FDA Table 18: Number and Risk of Melanomas in the Immediate and Delayed Start Groups by Time Strata from Time of *Initial Rasagiline Exposure*

Number of Melanomas Per Treatment Group	**0-6 Months**	**6 –12 Months**	**12-18 Months**	**18-24 Months**	**>24 Months**
PRESTO Immediate	3 (1%)	2 (0.6%)	1 (0.3%)	0	0
PRESTO Delayed	1 (0.6%)	0	0	0	0
TEMPO Immediate	1 (0.4%)	0	2 (0.8%)	0	6 (2%)
TEMPO Delayed	0	0	0	0	1 (0.7%)
Total Immediate	**4 (0.7%)**	**2 (0.3%)**	**3 (0.5%)**	**0**	**6 (1%)**
Total Delayed	**1 (0.3%)**	**0**	**0**	**0**	**1 (0.3%)**

Risk (Percent) shown in parentheses. The denominator for the risk calculations was the number of subjects entering the placebo-controlled (initial) phase of the trials (PRESTO: 159 Placebo [Delayed Group], 313 Rasagiline; TEMPO: 138 Placebo [Delayed Group], 266 Rasagiline).

[31] As noted in the study summaries in Section 2.3.2, subjects in PRESTO were older and had more advanced Parkinson's disease than subjects in TEMPO, providing an explanation for the higher adverse event and discontinuation rates in PRESTO compared to TEMPO.

The preceding table demonstrates a substantial difference in the timing of melanoma diagnosis within the two trials, with melanomas being diagnosed earlier in PRESTO, and considerably later in TEMPO. The most readily apparent explanation for this is the timing of the initiation of melanoma screening within the rasagiline development program between October and December 2001. The TEMPO study was already well underway by this time (the open-label phase began in 1999), and no subject in the ongoing TEMPO extension had a formal dermatological screening examination prior to beginning treatment. The PRESTO study was conducted between December 2000 and January 2003, however, so 42 to 44% of PRESTO patients received dermatological screening prior to treatment. The initiation of melanoma screening lead to an increase in the number of melanomas identified,[32] apparently due to a surveillance bias. The active dermatological screening thus acts as a confounder in the observation of melanoma timing throughout the studies, and may obscure any potential effect of latency or cumulative rasagiline dose, especially in TEMPO in which the screening commenced later in the study period.

Reviewer comment: *It has been hypothesized that the initiation of screening later in the TEMPO study than in PRESTO would lead to a higher proportion of* ***invasive*** *melanomas detected within the TEMPO study. However, the experience of TEMPO and PRESTO are not demonstrative of this hypothesis, as the number of invasive and in situ melanomas were essentially equivalent in both studies (TEMPO: 5 invasive melanomas, 6 in situ melanomas, PRESTO: 4 invasive melanomas, 3 in situ melanomas).*

Because the above table measures the time in months from the initial *rasagiline* exposure, the leading placebo time in the delayed start group is not accounted for. In the following table, the number and risk of melanoma is calculated from the time of the first study dose, whether rasagiline or placebo, thus including the placebo period.

FDA Table 19: Number and Risk of Melanomas in the Immediate and Delayed Start Groups by Time Strata from Time of *First Study Dose (Placebo or Rasagiline)*

Number of Melanomas Per Treatment Group	**0-6 Months**	**6 –12 Months**	**12-18 Months**	**18-24 Months**	**>24 Months**
PRESTO Immediate	3 (1%)	2 (0.6%)	1 (0.3%)	0	0
PRESTO Delayed	0	0	1 (0.6%)	0	0
TEMPO Immediate	1 (0.4%)	0	2	0	6 (2%)
TEMPO Delayed	0	0	0	0	1 (0.7%)
Total Immediate	**3 (0.5%)**	**2 (0.3%)**	**3 (0.5%)**	**0**	**6 (1%)**
Total Delayed	**1 (0.3%)**	**0**	**1 (0.3%)**	**0**	**1 (0.3%)**

[32] The increase in the melanoma detection rate following the commencement of active dermatologic screening is discussed in Section 5.4.2 of the Rasagiline NDA Safety Review, prepared by M. Lisa Jones, dated July 5, 2004.

Risk (Percent) shown in parentheses. The denominator for the risk calculations was the number of subjects entering the placebo-controlled (initial) phase of the trials (PRESTO: 159 Placebo [Delayed Group], 313 Rasagiline; TEMPO: 138 Placebo [Delayed Group], 266 Rasagiline).

Reviewer comment: *There is relatively little difference between the tables calculated from first rasagiline exposure (Table 17) and first study drug (rasagiline or placebo)(Table 18). This is reflective of the small (n=2) number of melanomas in the delayed start group, in which placebo treatment preceded rasagiline exposure.*

The two tables demonstrate that within most of the time period sub-analyses (with the exception of >24 months time period) the difference in risk between the immediate and delayed start groups is not particularly large.

2.3.5 FDA Conclusions on Immediate/Delayed Start Comparison

As an overall conclusion on the delayed versus immediate start comparison, although the analysis has generated some intriguing speculation into the potential mechanisms behind the three-fold higher melanoma rate in the immediate start group, this relatively simple comparison is not particularly informative regarding the factors which may contribute to this elevation. The degree of the melanoma difference between the two groups is also uncertain, as the confidence intervals between the two groups share considerable overlap.

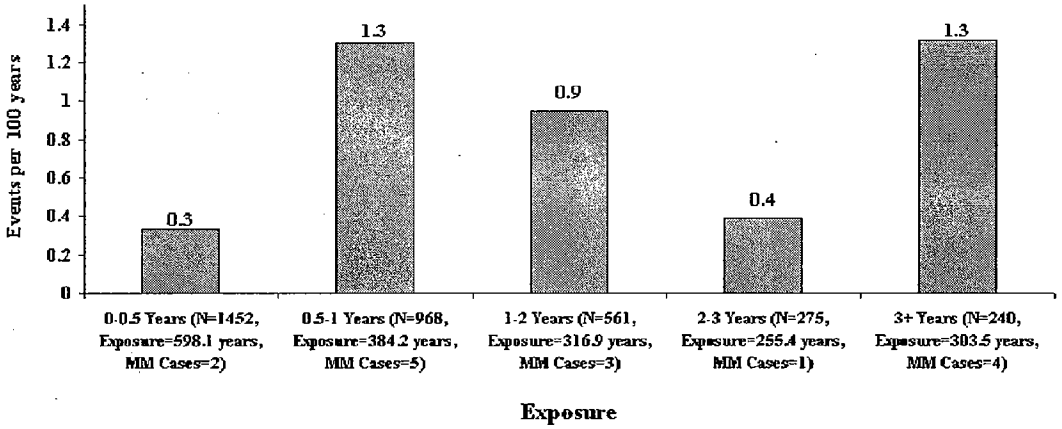
2.3.6 Prior Analysis of the Relationship between Rasagiline Exposure and Melanoma Development

In the sponsor's presentation on melanoma within the original ISS[33], Teva submitted a bar-graph figure illustrating melanoma cases per 100 patient-years across various time strata. As initially constructed by the sponsor, the figure credited person-years only to the stratum corresponding to the subject's full duration of exposure (i.e., all the time for a subject participating in the study for 1.5 years was included within the 1-2 year stratum.) As subjects have the opportunity to develop an AE (in this case, melanoma) for the entire period they are exposed to drug, the more appropriate method for presenting this figure is to include the exposure a patient contributes to each duration stratum.[34] At the request of the FDA the sponsor repeated the above analysis using the correct method of attributing exposure time.

FDA Figure 1: Total Melanoma Events per 100 Subject-Years by Time Exposure Categories (Adapted from Sponsor Figure 2, Presented in Section 5.4.5 of the Rasagiline NDA Safety Review, Prepared by M. Lisa Jones, Dated July 5, 2004)

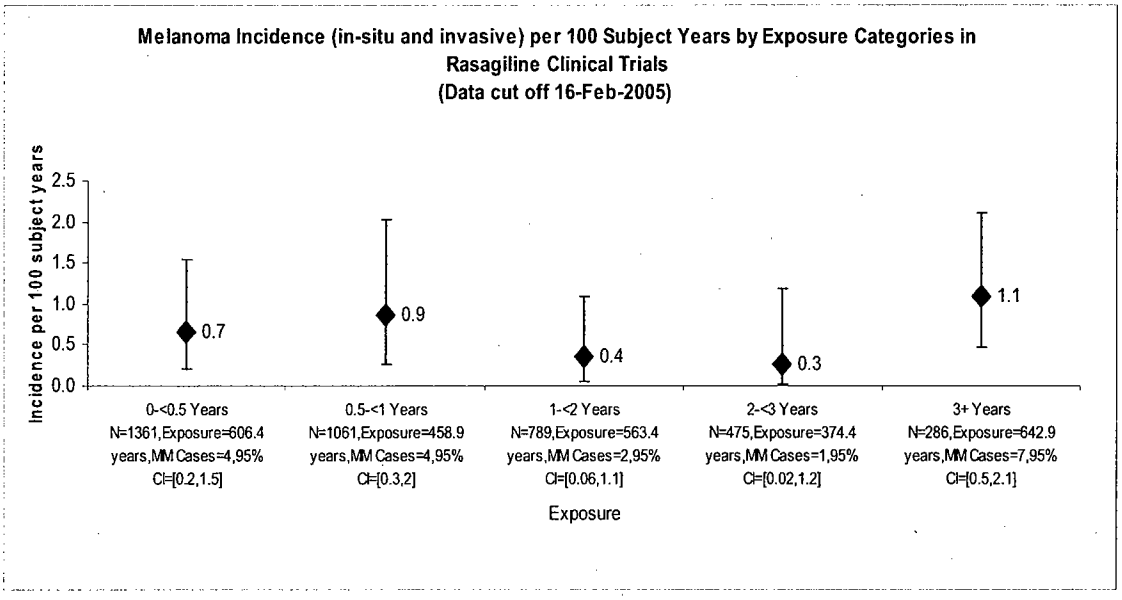
[33] ISS Appendix 18.3 Figure 2
[34] For example, a patient who remains in the study for 1.5 years would contribute 0.5 years to the first six month strata, 0.5 years to the second six month strata, and 0.5 years to the 1-2 year strata.

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)



As more rasagiline exposure had accumulated since the original NDA, the sponsor was asked to update the figure above to reflect the additional exposure time and to provide confidence intervals for each time epoch. Teva provided[35] the following two figures in response to the FDA request.

FDA Figure 2: Total Melanomas Per 100 Subject-Years by Exposure: Updated Version with Follow-Up to Three of Three-Plus Years

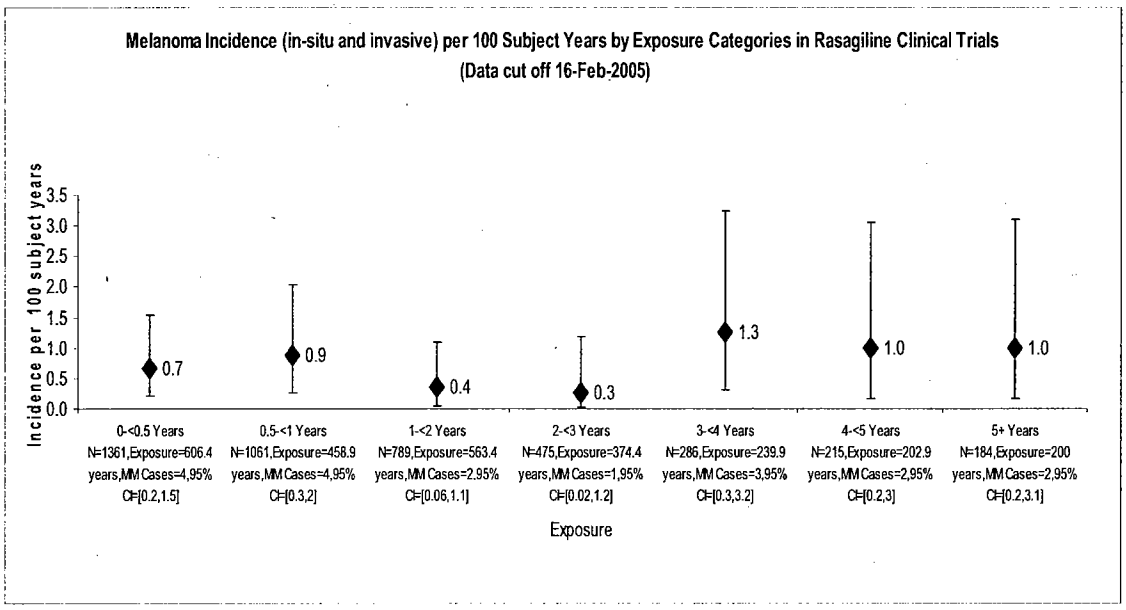


* Each subject is counted once - subject No. 64 as invasive.

[35] Received via electronic mail, May 11, 2005.

* Only PD patients (N=1361) were included.

FDA Figure 3. Total Melanomas Per 100 Subject-Years by Exposure: Updated Version with Follow-Up to Three of Five-Plus Years



* Each subject is counted once - subject No. 64 as invasive.
* Only PD patients (N=1361) were included.

Reviewer comment: *Although the number of melanomas per 100 PYs is somewhat increased in the later time periods (specifically in Figure 3 for the time periods of three to five-plus years), the confidence intervals between the various time periods demonstrate considerable overlap. In addition, the decreased number of subjects reaching the latter time periods contributes to a widened confidence interval and increased uncertainty of the level of elevation. There therefore does not appear a strong trend of increasing melanoma occurrence with cumulative rasagiline exposure over time as per this analysis.*

2.4 Melanoma Biopsies: Central Versus Local Laboratory Diagnosis

As discussed in Section 7 below on the incomplete attribution of adverse events, the sponsor reported that subject TVP-1012/135 #109 had a skin lesion which was initially diagnosed as a melanoma in situ by a local pathology laboratory, and was later reassessed as a melanocytic nevus (compound type) by the central laboratory. This prompted an e-mail request to the sponsor for clarification of the re-classification process, and information on any other subjects for which the local and central laboratory diagnoses were discrepant. The sponsor responded[36] that, as per pre-defined study protocol, the final decision regarding the lesion diagnosis was made by the central laboratory, which

[36] E-mail communication from Teva received February 18, 2005.

utilized a standardized terminology for diagnoses. Because assessment by the central laboratory was not immediate, for patient safety Teva stated that all specimens were also evaluated by a local lab. Teva reported that in the majority of cases the final central laboratory diagnosis matched the local laboratory assessment. However, for 14 out of 751 cases (1.9%) through August 2004 there was a discrepancy between the diagnosis made by the central and the local laboratory. Teva noted that both the local and central laboratory pathologists were blinded as to treatment group. The sponsor provided the following additional information on the fourteen discrepant cases:

FDA Table 20: Comparison of Local Laboratory Versus Central Laboratory Diagnoses for Dermatologic Surveillance Biopsies with Discrepant Results

	Subject #	Study #	Submitting Pathologist's Diagnosis	Central Laboratory Diagnosis
1.	103	233	Focal early Melanoma in situ	Nevus
2.	109	135	Melanoma in situ	Nevus
3.	117	135	Melanoma	Nevus
4.	118	135	Melanoma	Nevus
5.	120	233	Melanoma in situ	Atypical Melanocytic Nevus
6.	196	135	Melanoma	Nevus
7.	257	133	Lentigo maligna	Nevus
8.	15406	122	Melanoma in situ	Dysplastic nevus
9.	322	233	Melanoma in situ cannot be ruled out	Nevus
10.	546	233	Early melanoma in situ cannot be ruled out	Nevus
11.	64	233	Melanocytic nevus	Melanoma
12.	116	233	Melanocytic nevus	Melanoma in situ
13.	209	133	Nevus with atypia	Melanoma
14.	494	135	Atypical melano hyperplasia	Melanoma in situ

Reviewer comment: *Of the 14 discrepant cases above, in four cases the central laboratory classified the biopsy as a more advanced lesion (i.e., melanoma) than did the local laboratory reading, and these four have been included among the 24 cases of melanoma summarized in the preceding table. In ten cases, however, the central lab "down-graded" the lesion from a melanoma to a nevus. Although this distribution could be expected infrequently based on chance variation (Exact binomial, P [10; 0.5,14] = 0.06), the table above illustrates that there is a potential for cases of melanoma to be "lost" due to discrepant readings.*

The DNDP Safety Team consulted dermatologist Dr. Patricia Brown of the Division of Dermatologic and Dental Drug Products (FDA) for assistance in determining whether the diagnostic discrepancies described above would be considered unusual in clinical

histopathological practice. Dr. Brown cited several studies on inter-rater reliability for melanoma diagnosis in support of a preliminary conclusion that this degree of disparity is within the range of general diagnostic accuracy. Dr. Brown specifically referenced a study by Weinstock et al.[37], which examined the agreement of a panel of five dermatopathologists and two melanoma specialists in diagnosing 112 pathology slides of melanocytic nevi and melanomas. The Pearson correlation between each of the five dermatopathologists and the mean of the two melanoma specialists was 0.67 to 0.84. Although this level of agreement falls into the substantial to excellent range, the 1.9%[38] incidence of discordant diagnoses between the local and central pathology labs in the rasagiline development program is consistent with general diagnostic accuracy.

2.5 Occurrence of Invasive Melanomas in the Development Program Despite Regular Dermatologic Screening

Following the institution of a dermatologic screening program for melanoma within the rasagiline development program, two subjects were diagnosed with invasive melanomas.

1. **PRESTO Ext. #271**: This 68 year old man was diagnosed with a superficial spreading melanoma (invasive to a depth of 1.1 mm) during his sixth dermatologic examination, when the subject had been enrolled in the study for 14 months (Date of diagnosis: [redacted].[39] As per the sponsor narrative[40], the subject had a history of basal cell carcinoma prior to study entry and two previous biopsies (in 2001) during the study screening program (both were diagnosed as melanocytic nevi). The subject was also noted to have actinic keratosis of the scalp during previous study screenings.
2. **TEMPO Ext. #544:** This 71 year old woman was diagnosed with a focal malignant melanoma (invasive to 1.7 mm) during her fourth dermatologic examination, when the subject had been enrolled in the study for 47 months. As per the sponsor narrative, she did not have a history of skin cancers prior to study entry. Her previous study screening examinations were notable for multiple actinic keratoses, but she apparently had no suspicious lesions biopsied prior to her diagnosis with melanoma.[41]

***Reviewer comment**: These cases may represent formerly in situ lesions that were missed on earlier screening examinations, as the sensitivity of melanoma screening has been estimated at only 70.1%, with a specificity of 99.4% and a positive predictive value of 60.7%.[42] In addition, approximately 10 to 15% percent of melanomas are of the nodular*

[37] Weinstock MA et al. Reliability of the histopathologic diagnosis of melanocytic dysplasia. The Dysplasia Nevus Panel. Arch Dermatol. 1997 Aug.;133(8):953-8.
[38] Through August 2004 there was a discrepancy between the diagnosis made by the central and the local laboratory in 14 out of 751 cases (1.9%).
[39] Rasagiline NDA Primary Safety Review, Section 5.5.3, pg. 130.
[40] 120 Day Safety Update, Integrated Summary of Safety, Appendix 10.4, pg. 242.
[41] 120 Day Safety Update, Integrated Summary of Safety, Appendix 10.4, pg. 299.
[42] Wolf IH et al. Sensitivity in the clinical diagnosis of malignant melanoma. Melanoma Res. 1998; Oct,8(5): 425-9.

subtype, which lacks an extended superficial growth phase and is invasive essentially from the time it develops. Therefore, the identification of two invasive melanomas during active dermatological screening among 24 total melanomas may not be an unexpected finding. However, the sponsor narratives do not classify these cases as nodular melanomas. These cases are a reminder that dermatologic screening, even with frequent examinations, will not prevent 100% of invasive melanomas. However, I believe that this is attributable to the nature of melanoma and its screening, and is unrelated to rasagiline exposure.

2.6 FDA Recommendation for a Large Simple Study of Rasagiline and Melanoma

2.6.1 FDA Request in Approvable Letter

> "Finally, we recommend that you conduct a large simple randomized controlled trial, postapproval, to compare melanoma rates between Parkinson's disease patients who are exposed and unexposed to rasagiline. A randomized controlled trial is suggested as this design has the greatest likelihood of producing equivalent treatment and control groups. Parkinson's disease patients (both newly diagnosed and those already on levodopa therapy) could be recruited through their outpatient providers, but it would be beneficial to stratify patients by monotherapy or adjunctive therapy. To control for geographic variation in background rates, it is recommended that similar numbers of rasagiline exposed and unexposed subjects be drawn from various geographic areas within North America. Given the much lower risk of melanoma among persons with increased melanin content in their skin, subject recruitment should be restricted to Caucasian subjects. Baseline information for cohort members should 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. You should conduct active screening for melanoma (once every six months), as detection is likely to vary in different clinical settings. Upon study entry, subjects should also be given basic information on skin cancers and self-examination for suspicious lesions. Other aspects of trial design, including sample size and duration, can be decided upon through further discussion between TEVA and DNDP." (NDA 21-641, Rasagiline Approvable Letter, pg. 5)

2.6.2 Sponsor Response

The sponsor did not address the request for a Phase IV study within a distinct section of their response to the Approvable letter, but Teva did state that they were considering "conducting a post-approval study to assess melanoma rates in Parkinson's disease patients who are exposed and unexposed to rasagiline." No further information regarding these considerations or the timing of updates was provided (Response to Action Letter: Melanoma, pg. 3).

Reviewer comment: *As discussed in the primary NDA safety review (Section 5.5), the design and time course of the pivotal studies within the NDA resulted in the majority of melanomas being diagnosed in extension studies without a concurrent control group unexposed to rasagiline. This necessitated use of external comparison groups to assess whether the number of melanomas diagnosed was more than would be expected for this population. Use of external comparator groups has a number of limitations in general, and particularly so in the case of melanoma assessment in the rasagiline development program: potential confounders for melanoma in the development program population included age, geographic variation, Parkinson's disease and its treatment, and that participants enrolled in the rasagiline development program after the identification of the melanoma signal underwent regular screening for melanoma. External comparison groups were identified that could address one or two of these potential confounders, but no comparison group was found that adequately replicated all or even a majority of them. This undermines the strength of the conclusions that can be reached from such comparisons. These same limitations apply to the two cohort studies conducted by the sponsor, which also lacked concurrent control groups.*

The safety analysis to date has attempted to compensate for this lack of a control group through multiple analyses addressing questions indirectly related to a potential relationship between melanomas and rasagiline exposure. Some of these analyses have been supportive of a role for rasagiline and melanoma development, and some have not. Because it is not possible to know the exact applicability and respective weight that should be assigned to these various surrogate analyses, it is difficult to assess the totality of the data to reach a final conclusion. Although other manipulations of the current data are possible, the highest yield analyses have essentially been exhausted. I therefore now believe that these analyses and any further analyses of the data at hand will not further elucidate the safety of rasagiline with respect to melanoma.

For these reasons, I recommend that a large simple study, such as the requested Phase IV study described in the Approvable Action letter, be conducted to provide a more thorough understanding of the association between rasagiline and melanoma. Furthermore, in light of the above conclusion that existing data cannot provide a satisfactory conclusion on the matter, this study should be conducted ***prior*** *to drug approval, as opposed to Phase IV as previously requested in the Approvable Action letter. The recommendation for completing a melanoma study prior to approval is strengthened by the pre-clinical findings regarding melanoma and rasagiline, which included:*

- *The rare occurrence of a melanoma in one rasagiline-treated albino rat out of approximately 60 rats dosed (Background rate of melanomas in albino rats estimated at 0.14%)*
- *An association between rasagiline treatment and lung cancer in mice*
- *Evidence of rasagiline genotoxicity in three separate assays*

3. EXPANDED ECG ANALYSIS

3.1 Expanded Rasagiline Monotherapy (TEMPO) ECG Analysis

3.1.1 FDA Question in Approvable Letter

"Guidance is evolving in CDER (and ICH) requesting that all new drug products in development be adequately evaluated to characterize the effect of the drug on cardiac repolarization. The "thorough QT" study is described in a recently completed ICH Step 2 guidance (ICH-E 14). Given that the rasagiline development program did not include an adequate assessment of the effect of rasagiline on the QT/QTc interval (or the other ECG parameters, for that matter), a two-pronged approach is requested.

- In order to understand the effect of rasagiline on the ECG as measured in Parkinson's disease (PD) patients on rasagiline monotherapy, we request that the ECGs from TEMPO be centrally re-read and analyzed in a manner similar to how the PRESTO and LARGO studies in Cohort 2 have been analyzed.
- In order to understand the effect of rasagiline on cardiac repolarization in general, we request that you conduct a "thorough QT" study similar to the one described in the concept paper referenced above. Whether this needs to be completed prior to approval will depend on the TEMPO analysis and overall results in all three controlled studies. However, you may wish to incorporate EKG monitoring into the tyramine challenge study, as with blood pressure monitoring (see below).

It is also requested by the Office of Clinical Pharmacology and Biotherapeutics that an ECG dataset be created for subjects in TEMPO, PRESTO and LARGO that would contain the following variables: rasagiline dose, concentration time on rasagiline, heart rate (HR), RR (I/HR), QT, and all demographic covariates (i.e., sex, age, etc.)." (NDA 21-641, Rasagiline Approvable Letter, pg. 6).

3.1.2 Sponsor Response

3.1.2.1 General Description of Methods

Teva reported that, as per the FDA request in the Approvable Letter, all ECG tracings from the placebo-controlled phase of the monotherapy study TEMPO were re-read by a centralized facility (, and analyzed in a manner similar to the adjunctive therapy studies PRESTO and LARGO in of the original ISS[43].

For the descriptive statistics analysis, Teva stated that heart rate, PR, QRS and QT intervals were each tabulated as the mean of three individual measurements. Teva defined the potentially clinically significant (PCS) absolute QTc was as a QTcBazett (QTcB) of greater than 450 msec for males and greater than 470 msec for females. The sponsor reported that, as per the FDA's suggestion, an additional outlier analysis was

[43] ISS = Integrated Summary of Safety

performed for both absolute QTcB and absolute QTc Fridericia (QTcF) greater than 500 msec (Response to Approvable Letter: ECG, pg. 6).

Teva commented that although a QTcB change from baseline of between 30 to 60 msec represents a potential drug effect, a QTcB change from baseline of greater than 60 msec is of clear concern. The sponsor stated the QTcB data would therefore be analyzed "accordingly," and an additional analysis of change from baseline QTcF of greater than 60 msec was included (Response to Approvable Letter: ECG, pg. 6).

The sponsor explained that in their assessment of the *overall* effect of rasagiline therapy on the ECG, the numerical and categorical data generated from the placebo-controlled phases of the monotherapy TEMPO study and the adjunctive therapy PRESTO and LARGO studies were combined. Teva stated that the 0.5 mg group of the PRESTO study was compared to the 1 mg and placebo groups previously reported for Cohort 2 in the original ISS (Response to Approvable Letter: ECG, pg. 6).

3.1.2.2 Monotherapy Descriptive Statistics

Teva reported that no prominent differences were present between the treatment groups (rasagiline 1 mg, rasagiline 2 mg and placebo) in the monotherapy study TEMPO for heart rate, PR and QRS interval (Response to Action letter: ECG, pg. 6).

Reviewer comment: *I reviewed the sponsor table (Post-Text Table 1) summarizing the descriptive statistics for ECG parameters in the monotherapy study TEMPO, and concur with the sponsor's assessment that no prominent differences or dose response patterns were apparent.*

3.1.2.3 Monotherapy QT Interval

The sponsor noted that the QTcB mean interval change from screening was 1.3 msec for the rasagiline 1 mg group, -3.6 msec for the 2 mg group and -0.2 msec for the placebo group. QTcF mean interval change from screening ECG was 2.0 msec for the rasagiline 1 mg group, -0.1 msec for the rasagiline 2 mg group and 0.7 msec for placebo. Citing the ICH E14 guideline document on QT/QTc evaluation, Teva commented that drugs such as rasagiline that prolong the mean QT/QTc interval by approximately 5 msec or less do not appear to cause Torsades de Pointes (TdP) (Response to Approvable Letter: ECG, pg. 7).

FDA Table 21: QTc Mean Interval Descriptive Statistics of Change from Screening to Last Observed Value for Monotherapy Study TEMPO (Adapted from Sponsor Table 1, Response to Approvable Letter, pg. 7)

TVP-1012/232 (TEMPO) Placebo Controlled Phase		Rasagiline 1 mg	Rasagiline 2 mg	Placebo
QTc Mean Interval (Bazett) (msec) Change from Screening	N	121	123	127
	Mean	1.3	-3.6	-0.2
	Std	18.6	20.2	21.9
	Median	2.0	-4.0	-1.0
	Min	-60	-53	-65
	Max	41.0	57.0	68.0
QTc Mean Interval (Fridericia) (msec) Change from Screening	N	121	123	127
	Mean	2.0	-0.1	0.7
	Std	15.9	18.9	17.9
	Median	2.0	0.0	-1.0
	Min	-48	-57	-51
	Max	43.0	58.0	59.0

Reviewer comment: *As per the sponsor's title for the table above, these values appear to represent the change from screening ECG to the Last Observed Value (LOV) ECG. The TEMPO study report (pg. 60) states that "ECG was carried out at screening, Week 14, termination of the placebo-controlled phase (Week 26), study drug discontinuation (Week 52) and at a follow-up visit (Week 58)." The sponsor was asked "Were subjects still receiving treatment with rasagiline at the time of the LOV ECG, and if not, how long had they been untreated?" to which Teva responded[44] that "All 133 patients who had the follow-up visit (Week 58) were not receiving rasagiline at that time." The sponsor reported that subjects had been off rasagiline a mean of 47 days between the Week 52 Visit and Week 58 visit.*

The sponsor was also asked to re-calculate QT interval changes from baseline to ***Maximal Observed Value*** *(as opposed to LOV), which they presented as per the tables below:*

FDA Table 22: TEMPO Placebo-Controlled Phase: QTc Mean Interval: Descriptive Statistics of Change from Screening to Maximal Observed Value (***Bazett***)(msec) (Sponsor Table 2, Response to Safety Reviewer Question, Received via Electronic Mail on April 18, 2005)

[44] Sponsor response received by e-mail on April 18, 2005.

TVP-1012/232 Placebo Controlled Phase		Rasagiline 1 mg	Rasagiline 2 mg	Placebo
QTc Mean Interval (Bazett) (msec) - Maximal Decrease	N	73	84	79
	Mean	16.6	18.0	18.6
	Std	10.9	12.8	13.5
	Median	16.0	15.0	16.0
	Min	1	0	0
	Max	60	53	65
QTc Mean Interval (Bazett) (msec) - Maximal Increase	N	81	74	74
	Mean	16.2	17.0	20.2
	Std	12.2	14.9	14.8
	Median	14.0	13.5	18.0
	Min	0	0	0
	Max	61	74	68

FDA Table 23: TEMPO Placebo-Controlled Phase: QTc Mean Interval: Descriptive Statistics of Change from Screening to Maximal Observed Value (***Fridericia***)(msec)(Sponsor Table 3, Response to Safety Reviewer Question, Received via Electronic Mail on April 18, 2005)

TVP-1012/232 Placebo Controlled Phase		Rasagiline 1 mg	Rasagiline 2 mg	Placebo
QTc Mean Interval (Fridericia) (msec) – Maximal Decrease	N	75	75	74
	Mean	12.9	15.8	14.7
	Std	9.3	11.6	11.2
	Median	12.0	14.0	11.5
	Min	0	0	0
	Max	48	57	51
QTc Mean Interval (Fridericia) (msec) – Maximal Increase	N	83	79	77
	Mean	13.3	17.3	16.8
	Std	10.5	13.8	13.0
	Median	11.0	16.0	14.0
	Min	0	0	0
	Max	43	76	59

***Reviewer comment**: The sponsor's response has been unclear as to whether subjects were still being treated with rasagiline at the time of the LOV ECG: the TEMPO study report stated that the last ECG was obtained at a follow-up visit at Week 58, but the sponsor's reply noted that 133 patients attended the Week 58 visit, fewer than the 371 patients for which data was summarized in Table 20 above (which was labeled as LOV ECG data). A follow-up question has been sent to the sponsor to clarify the matter. However, as noted by the sponsor, the data to Maximum Observed Value, as shown in*

Tables 21 and 22 above, demonstrate a similar change from baseline for the two rasagiline treatment (1mg and 2mg) and placebo groups.

3.1.2.4 Monotherapy Shift Analysis for Categorical Data

Teva summarized the shift analysis[45] for the categorical ECG parameters of U wave, arrhythmia, conduction, morphology, ST segment, T wave, rhythm and myocardial infarction in the following table (Response to Action Letter: ECG, pg. 6).

FDA Table 24: Shift Analysis of ECG Results for Monotherapy Study TEMPO (Adapted from Sponsor Post-Text Table 2, Response to Approvable Letter: ECG, pg. 21)

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[45] Shift analysis refers to shifts or changes in these parameters between the categories of present/absent or normal/abnormal.

TVP-1012/232 (TEMPO) Placebo Controlled Phase		Rasagiline 1 mg		Rasagiline2 mg		Placebo	
		N	%	N	%	N	%
Arrhythmia Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	127	94.8	125	94.7	130	94.2
	Present to Absent	2	1.5	.	.	2	1.4
	Absent to Present	1	0.7	3	2.3	4	2.9
	All	134	100.0	132	100.0	138	100.0
Conduction Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	129	96.3	126	95.5	134	97.1
	Abnormal to Normal	.	.	1	0.8	1	0.7
	Normal to Abnormal	1	0.7	.	.	.	.
	Change in Characteristics	.	.	1	0.8	1	0.7
	All	134	100.0	132	100.0	138	100.0
Morphology Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	130	97.0	128	97.0	136	98.6
	All	134	100.0	132	100.0	138	100.0
Myocardial Infarction Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	130	97.0	127	96.2	136	98.6
	Absent to Present	.	.	1	0.8	.	.
	All	134	100.0	132	100.0	138	100.0
Rhythm Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	129	96.3	119	90.2	125	90.6
	Abnormal to Normal	1	0.7	5	3.8	3	2.2
	Normal to Abnormal	.	.	4	3.0	8	5.8
	All	134	100.0	132	100.0	138	100.0
ST Segment Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	129	96.3	128	97.0	136	98.6
	Abnormal to Normal	1	0.7	.	.	.	.
	All	134	100.0	132	100.0	138	100.0
T Waves Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	124	92.5	124	93.9	132	95.7
	Abnormal to Normal	2	1.5	2	1.5	2	1.4
	Normal to Abnormal	3	2.2	1	0.8	2	1.4
	Change in Characteristics	1	0.7	1	0.8	.	.
	All	134	100.0	132	100.0	138	100.0
U Waves Shift	Missing Data	4	3.0	4	3.0	2	1.4
	No Change	130	97.0	128	97.0	136	98.6
	All	134	100.0	132	100.0	138	100.0

The sponsor stated that the incidence of abnormal results for these parameters was either highest in the placebo group, or similar in all treatment groups. Teva described the abnormalities occurring among rasagiline-treated subjects as follows:

- A single shift to abnormal conduction was seen in patient TVP-1012/232 #143 (receiving rasagiline 1 mg) who experienced a new first degree AV block (PR interval increase from 162 to 214 msec) recorded about two weeks after he withdrew from the study due to a reversible ischemic neurologic deficit (RIND).
- A single myocardial infarction shift was seen in patient TVP-1012/232 #216, receiving rasagiline 2 mg. The sponsor reported that this patient's ECGs were originally reported as normal within the TEMPO study report. However, subsequent

assessment by ← letermined interventricular conduction delay (IVCD) on screening ECG, and right bundle branch block (RBBB), left atrial hypertrophy (LAH) and changes consistent with inferior myocardial infarction on two later ECGs. Teva stated that no clinical symptoms or signs were noted and that the patient completed the TEMPO study without reporting any cardiovascular AEs (Response to Approvable Letter: ECG, pg. 7).

Teva stated that for the category of QTcB greater than 450 msec for males and greater than 470 msec for females, shifts from non-PCS to PCS occurred more often in the placebo group (3.1%) than in the rasagiline groups (0.8%)(Response to Approvable Letter: ECG, pg. 7). In the category of change in QTcB of ≥ 30 and ≤ 60 msec, Teva likewise reported that the incidence was also higher for placebo (13.4%) than for rasagiline 1 mg (9.1%) and 2 mg (9.8%). Teva further noted that change in QTcB from screening of > 60 msec occurred with comparable incidence for placebo and rasagiline 1 mg (one patient each, 0.8%), and was seen in two patients on rasagiline 2 mg (1.6%). Narratives for these four patients are provided in Attachment 12.7 of this review The sponsor reported that none of the patients met PCS criteria for absolute QTcB or QTcF >500 msec (Response to Approvable Letter: ECG, pg. 8).

3.2 Sponsor Overall ECG Assessment

As described in Section 3.1.2.1, the sponsor analyzed the overall ECG effect by combining data from the monotherapy (TEMPO) and adjunctive therapy (PRESTO and LARGO) studies. Teva stated that no prominent differences were present between the treatment groups (rasagiline 0.5 mg, 1 mg, 2 mg and placebo) for heart rate, PR and QRS intervals.

***Reviewer comment**: I reviewed these data (Post-Text Table 3) and agree that there were no significant differences consistent with a dose-response pattern between the rasagiline and placebo treatment groups.*

The sponsor further stated that mean change from screening for the corrected QT interval (QTcB and QTcF) demonstrated no consistent effect attributable to rasagiline, as shown in the following table (Response to Approvable Letter: ECG, pg. 12).

FDA Table 25: Descriptive Statistics of Change from Screening to Last Observed Value in QTc Mean Interval (Adapted from Sponsor Table 8, Response to Approvable Letter: ECG, pg. 12)

TVP-1012 Placebo-Controlled Phase III Studies (TEMPO, PRESTO and LARGO)		Rasagiline 0.5 mg (N=164)	Rasagiline 1 mg (N=514)	Rasagiline 2 mg (N=132)	Placebo (N=526)
QTc Mean Interval (Bazett) (msec) Change from Screening	N	156	477	123	494
	Mean	2.1	1.2	-3.6	0.2
	Std	20.9	22.9	20.2	22.2
	Min	-49	-92	-53	-65
	Max	73.0	64.0	57.0	71.0
QTc Mean Interval (Fridericia) (msec) Change from Screening	N	156	477	123	494
	Mean	1.8	2.3	-0.1	0.6
	Std	18.5	19.9	18.9	19.0
	Min	-44	-74	-57	-62
	Max	73.0	52.0	58.0	59.0

The sponsor stated that for arrhythmia, conduction and rhythm shifts the placebo treatment group had similar or greater incidence as compared to the rasagiline-treated groups. Teva asserted that the higher incidence of ST segment shifts (n=5, 3.0%) and T wave (n=7, 4.3%) shifts in the 0.5 mg groups was not consistent at higher doses[46] and is therefore unlikely to be a drug effect. The sponsor stated that the three patients with morphology shifts had left ventricular hypertrophy (LVH) noted on ECG and were in the LARGO study.

The sponsor reported that three subjects experienced a myocardial infarction shift from absent to present. Teva stated that two patients from the LARGO study (both treated with rasagiline 1 mg) with shift to myocardial infarction were discussed in of the original ISS (Section 9.1.2.). The sponsor stated that information on the third subject (TEMPO subject #216 treated with 2 mg) was discussed above during the TEMPO ECG analysis (Sponsor report: Section 1.1.1.2) (Response to Approvable Letter: ECG, pg 12, pg. 24 [Post-Text Table 4]).

Teva stated that PCS results for rasagiline-treated subjects were compared to the placebo group as well as to the entacapone group of the LARGO study. The sponsor reported that in the category of QTcB greater than 450 msec for males and greater than 470 msec for females, shifts from non-PCS to PCS occurred more often in the placebo (n = 11; 2.2%) and entacapone (n = 6; 2.8%) groups than in the three rasagiline-treated groups (0.5 mg [n = 2; 1.3%], 1.0 mg [n = 6; 1.3%], and 2.0 mg [n = 1; 0.8%])(Response to Approvable Letter: ECG, pg. 13, pg. 25 [Post-Text Table 5]).

In the category of change in QTcB of ≥ 30 and ≤ 60 msec, the sponsor reported that the rasagiline treatment groups (0.5 mg [n = 15; 9.6%], 1.0 mg [n = 47; 9.8%] and 2.0 mg [n

[46] The number of subjects with morphology changes from normal to abnormal for the four treatment groups were placebo (n = 1; 0.2%), rasagiline 0.5 mg (n = 0), rasagiline 1 mg (n = 3; 0.6%) and rasagiline 2 mg (n = 0). For ST segment shifts, normal to abnormal changes were: placebo (n = 0), rasagiline 0.5 mg (n = 5, 3%), rasagiline 1 mg (n = 1, 0.2%), and rasagiline 2 mg (n = 0).

= 12; 9.8%]), the placebo group (n = 49; 9.9%) and the entacapone group (n = 28; 13.3%) had comparable incidence of about 10% (Response to Approvable Letter: ECG, pg. 13).

Teva stated that change in QTcB from screening of >60 msec occurred in a small number of patients with a comparable incidence for all groups: placebo (n = 4; 0.8%), rasagiline 0.5 mg (n = 1; 0.6%), rasagiline 1.0 mg (n = 2; 0.4%), rasagiline 2.0 mg (n = 2; 1.6%) and entacapone (n = 2; 0.9%). The sponsor noted that two[47] out of 840 rasagiline-treated patients (0.2%) also fit PCS criteria for QTcF change from screening >60 msec compared to none on placebo and 3/211 (1.4%) on entacapone (Response to Approvable Letter: ECG, pg. 13).

Teva stated that PCS absolute QTcB of >500 msec was seen in two patients and had been discussed in the original ISS:

- LARGO #16211(0.2%) on 1 mg with baseline left bundle branch block (LBBB)
- PRESTO #253 (0.6%) on 0.5 mg with pacemaker rhythm. Teva stated this subject also had QTcF>500.

Narratives for subjects with QTc >500 mesc and/or change from screening >60 msec are provided in Attachment 12.7 of this review.

3.3 Conclusions on Further ECG Studies

The sponsor concluded the analysis of the ECG data from the monotherapy (TEMPO) and the adjunctive therapy (PRESTO and LARGO) studies does not suggest a rasagiline-mediated effect on the ECG. In particular, Teva asserted that rasagiline does not appear to increase the risk for QTc interval prolongation (Response to Approvable Letter: ECG: pg. 18).

Regarding further studies to evaluate QT prolongation, Teva commented that "we trust that based on the ECG data…no additional study for the assessment of QT prolongation is needed."(Response to Approvable Letter: ECG, pg. 1).

Reviewer comment: *Based upon the above, I agree that rasagiline has not been demonstrated to affect ECG parameters to a clinically significant degree. Of particular importance is that measurements of QT interval prolongation were overall equivalent or less with rasagiline treatment than with placebo, for both the newly analyzed monotherapy subjects and the adjunctive therapy subjects. Although the ECG data collection and analysis performed by the sponsor could be improved in some regards (such as in recording information on ECG timing with respect to last study dose), the overall quality and quantity of the data, in combination with results noted immediately above, do not necessitate that additional studies be performed at this time. However,*

[47] The sponsor identified these two patients as PRESTO patient #253 (0.5 mg) with a pacemaker rhythm (discussed in the original ISS) and TEMPO patient #77 (2 mg), whose narrative is included in Attachment 12.7 of this review.

should the drug be approved, it will still need to be determined if a "thorough" ECG study should be conducted as a phase IV commitment given the requirements of the recently finalized ICH E14 guidance.

4. BLOOD PRESSURE

4.1 FDA Request in Approvable Letter

"We believe it is important to characterize changes in blood pressure timed to dosing, ideally capturing results at T_{max}, as well as at other appropriate times during the dosing interval. Such data was not collected in your trials. We ask that you collect such data for both resting BP and orthostatic BP. We believe this data can be collected within the tyramine challenge study requested above, with a placebo-control group and BP measured at multiple timepoints after dosing." (NDA 21-641, Rasagiline Approvable Letter, pg. 6)

4.2 Sponsor Response

Teva reported that data on blood pressure has been previously collected during Phase 1 studies. Teva stated that these studies, conducted in healthy subjects, assessed supine and standing systolic blood pressure (SBP) for both single dose and steady state (i.e., at least 7 days into dosing) rasagiline concentrations over the T_{max} interval (0.5-1 hour from dosing), as well as for various subsequent time points. The studies referred to by the sponsor are summarized in the table below. The sponsor stated that for the analysis of these studies orthostatic hypotension was defined as a drop in SBP of $\geq$ 20 mmHg after changing from a supine to standing position (Sponsor Approvable Letter Response: Blood Pressure, pg. 3).

FDA Table 26: Phase 1 Studies with Collection of Timed Blood Pressure Data: Rasagiline-Treated Subjects

Study	Subject Population	Dose of Rasagiline (mg)	Day of Dosing	Findings
Multiple Dose Studies				
CD596	18 males	2,5,10	10	**2 mg**: One subject exhibited orthostatic hypotension (with a SBP drop of 23 mmHg) at 0.5 and 12 hours. **5 mg**: One subject exhibited a 36 mmHg SBP drop at 8 hours. **10 mg**: One subject exhibited a 23 mmHg SBP drop at 8 hours.
424	8 Total: (5 males, 3 females)	1	7	One subject exhibited a 23 mmHg SBP drop at 4 hours.

425	8 Total: (6 males, 2 females)	1	7	No orthostatic hypotension was observed.
430	18 Total: (7 males, 11 females)	1	25	No orthostatic hypotension was observed.
Single Dose Studies				
P94159	12 males	1,2	1	No orthostatic hypotension was observed.
CC547	12 males	1,2,5,10,20	1	**1 mg:** One subject exhibited a 20 mmHg drop in SBP at 10 hours **2 mg:** Two subjects exhibited a drop in SBP greater than 20 mmHg (one with a 37 mmHg drop at 4 hours, one with a 22 mmHg drop at 10 hours)

FDA Table 27: Phase 1 Studies with Collection of Timed Blood Pressure Data: Placebo-Treated Subjects

Study	**Number of Placebo Subjects**	**Finding**
CD596	6 males	No orthostatic hypotension was observed.
430	6 Total: (4 males, 2 females)	One subject exhibited a 22 mgHg drop in SBP at one hour.
P94159	9 males	No orthostatic hypotension was observed.
CC547	12 males	One subject exhibited a 25 mmHg drop at 6 hours, which was close to persisting (19 mmHg) at 8 hours. Another subject exhibited a 22 mgHg drop at 1 hour.

Reviewer comment: *From comparison of rasagiline- and placebo-treated subjects in the tables above, it appears that studies 424 and 425 were not placebo-controlled. This was confirmed through referral to the original NDA review (Section 4.5). Therefore, two of the six studies above lacked placebo control.*

In their discussion, the sponsor noted that the majority of subjects exposed to rasagiline did not exhibit orthostatic hypotension (91% [69/76]). Of the seven subjects (9%) who did, the sponsor stated that in only one subject was the orthostatic hypotension observed near T_{max}, and that the effect on SBP appeared to be transient in all cases. Teva further stated that in four of the seven subjects, the decrease in SBP observed upon standing (up to 23 mmHg) was close to the lower limit defining an orthostatic response (20 mmHg). The sponsor reported that none of the decreases in standing SBP "manifested clinically," which Teva clarified as signifying that the subjects were asymptomatic and that no

adverse events were reported.[48] Finally, Teva noted that in the above studies, SBP was measured one minute after standing, rather than at two or three minutes as is currently accepted practice. The sponsor therefore asserted that several subjects may have experienced transiently low systolic blood pressure while still in the process of stabilizing their blood pressure in response to standing (Sponsor Approvable Letter Response: Blood Pressure, pg 5).

For the placebo-treated subjects in the studies above, three (11% [3/33]) met criteria for orthostatic hypotension. In one subject the drop in SBP occurred at one-hour post-dosing, which Teva noted roughly corresponded to the timing of the rasagiline T_{max}. In another subject Teva commented that it was "nearly" sustained for over two-hours (Sponsor Approvable Letter Response: Blood Pressure, pg. 5).

The sponsor concluded by asserting that based on the characterization of BP and dose levels presented above, rasagiline has been shown to be safe from a hemodynamic perspective at dose levels equal to and exceeding the 1 mg dose at which approval is sought (Sponsor Approvable Letter Response: Blood Pressure, pg. 5).

Reviewer comment: *The sponsor has cited data from pooled Phase 1 studies (encompassing a total of 76-rasagiline treated subjects) as an apparent substitute for the Approvable Letter request to collect additional blood pressure data (timed to dose) in a clinical trial setting. Although these studies could be considered supplemental data in support of the sponsor's assertion regarding rasagiline's hemodynamic safety, they do not suffice as a replacement for the data requested in the Approvable Letter: one third of the six studies lacked placebo control, and a single study of uniform design and dosing would be preferable to multiple pooled studies. In addition, these studies were conducted in healthy volunteers subjects, and not in Parkinson's disease subjects who may be more susceptible to a potential hypotensive effect of rasagiline.*

The sponsor is therefore requested to collect the additional data specified in the Approvable Action Letter. Given that the sponsor has provided some partial data in support of the hemodynamic safety of rasagiline, it is acceptable for this study be performed during the Phase IV period.

5. FLU SYNDROME

5.1 FDA Request in Approvable Letter

> "Flu syndrome and musculoskeletal adverse events were commonly reported with rasagiline treatment. In Cohort 1, the adverse events of flu syndrome, rhinitis, conjunctivitis, neck pain, arthralgia, arthritis, and joint disorder were all reported at least twice as frequently in the rasagiline group as in the placebo group. In

[48] Clarification received in an e-mail response (April 18, 2005) following an inquiry from this reviewer.

Cohort 2, this rasagiline-associated excess was observed for flu syndrome, neck pain, and arthralgia.

The frequency of these phenomena warrants further evaluation, as the NDA does not provide significant analysis or commentary on this potential safety signal. You should therefore perform additional analyses exploring the nature of this potential syndrome. We would be happy to discuss with you approaches to this re-analysis. In particular, we would be interested in your examining the frequency of amantadine as a concomitant PD therapy, as this drug is also an antiviral agent. An imbalance in the use of amantadine between treatment groups may have affected the occurrence of flu syndrome. In vitro or preclinical studies may be performed to investigate the role of cytokines as a potential mediator of these symptoms." (NDA 21-641, Rasagiline Approvable Letter, pg. 7)

5.2 Sponsor Response

5.2.1 Summary of Updated Results

For monotherapy subjects (Cohort 1), flu syndrome, rhinitis, conjunctivitis and musculoskeletal adverse events (specifically neck pain and arthitis) were among the most commonly[49] occurring adverse events. These and related adverse events for monotherapy subjects are presented in the following table (Rasagiline Approvable Safety Update, pg. 73). The sponsor noted that these results were based upon the "revised adverse event dictionary," in which several adverse events were re-coded as per FDA request (described in Section 4.4 of the NDA Safety Review.)

FDA Table 28: Flu Syndrome and Musculoskeletal Adverse Events by Treatment Group for Monotherapy Subjects (Cohort 1) (Adapted from Sponsor Table 44, Rasagiline Approvable Safety Update, pg. 74)

Pre-Approval Update of Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		Rasagiline 1 mg (N=149)			Rasagiline 2 mg (N=146)			Placebo (N=151)		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
FLU SYNDROME AND MUSCULOSKELETAL	-ALL	41	32	21.5	32	24	16.4	14	12	7.9
	ARTHRALGIA	14	11	7.4	20	15	10.3	8	6	4.0
	ARTHRITIS	4	3	2.0	.	.	.	1	1	0.7
	CONJUNCTIVITIS	4	4	2.7	1	1	0.7	1	1	0.7
	FLU SYNDROME	8	7	4.7	4	4	2.7	1	1	0.7
	JOINT DISORDER	3	2	1.3	3	2	1.4	1	1	0.7
	NECK PAIN	3	3	2.0	2	2	1.4	.	.	.
	RHINITIS	5	4	2.7	2	2	1.4	2	2	1.3

Reviewer comment: *As shown above, when evaluated against rasagiline 2 mg only joint disorder and arthralgia demonstrated a potential dose-response relationship.*

[49] Within the development program, "most common" adverse events were defined as those having an incidence of 2% or greater in the rasagiline 1 mg group, and at least twice that of the placebo group, while "common" adverse events were defined as those with an incidence of 2% or greater in the rasagiline 1 mg group, and numerically greater than placebo.

For adjunctive therapy subjects (Cohort 2), the sponsor noted that only arthralgia (12/380, 3.2% rasagiline 1 mg; 7/388, 1.8% placebo) met criteria for a common adverse event, although neck pain (4/380, 1.1% rasagiline 1 mg; 2/388, 0.5% placebo) and flu syndrome (6/380, 1.6% rasagiline 1 mg; 2/388, 0.5% placebo) were reported more frequently in the rasagiline than in the placebo treatment group.

Teva stated that for both the monotherapy (Cohort 1) and adjunctive therapy (Cohort 2) subjects, the majority of these adverse events were reported independently, meaning that they were not reported in association with each other or with the COSTART term "flu syndrome." However, four rasagiline-treated subjects in the monotherapy cohort, and two rasagiline-treated subjects (as well as one placebo-treated subject) in the adjunctive therapy cohort reported more than one of these adverse events. Among the six subjects reporting more than one of these adverse events, one[50] was considered a serious adverse event (neck pain due to cervical spinal disease requiring decompression) and one[51] resulted in study discontinuation (due to primarily abdominal complaints described as a flu-like syndrome)(Rasagiline Approvable Safety Update, pg. 74).

Reviewer comment: *The sponsor did not specify whether a time-frame was applied to subjects reporting the adverse events of interest in association with each other (i.e. if the adverse events needed to be reported within a day, a week or a month of each other to be considered associated.) In reviewing the description of the six subjects with multiple adverse events, however, the time period between events ranged from being reported the same day to within several months of each other.*

5.2.2 Analysis of Amantadine in Flu Syndrome

Teva stated that although anticholinergics were the only concomitant anti-Parkinson's disease medications allowed by protocol for monotherapy subjects, two patients in the rasagiline 1 mg group (1.3%) did receive amantadine during the placebo-controlled phase of the study. One of these subjects reported arthralgia, the other experienced flu syndrome. From these data the sponsor concluded that use of amantadine was not the cause of "decreased reporting of flu syndrome in the placebo group of this cohort" (Rasagiline Approvable Safety Update, pg. 75).

For adjunctive therapy subjects, the sponsor noted that approximately 25% of both treatment groups received amantadine. Teva stated that no rasagiline- or placebo-treated patients also receiving amantadine developed flu syndrome. However, for the 75% of subjects *not* receiving concomitant amantadine, the incidence of flu syndrome was 1.4% (4 subjects) in the rasagiline 1 mg group compared to 0.7% (2 subjects) in the placebo group (Rasagiline Approvable Safety Update, pg. 75).

[50] TVP-1012/133 #509
[51] TVP-1012/232 #604

FDA Table 29: Flu Syndrome and Musculoskeletal Adverse Events by Amantadine Hydrochloride (Adapted from Sponsor Table 46, Rasagiline Approvable Safety Update, pg. 75)

Pre-Approval Update of Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)				Placebo (N=388)			
		AMANTADINE HYDROCHLORIDE				AMANTADINE HYDROCHLORIDE			
		No		Yes		No		Yes	
		(N=285)		(N=95)		(N=289)		(N=99)	
		No. of Patients	% of Patients	No. of Patients	% of Patients	No. of Patients	% of Patients	No. of Patients	% of Patients
FLU SYNDROME AND MUSCULOSKELETAL	-ALL	16	5.6	4	4.2	7	2.4	3	3.0
	ARTHRALGIA	9	3.2	3	3.2	4	1.4	3	3.0
	FLU SYNDROME	4	1.4	.	.	2	0.7	.	.
	NECK PAIN	4	1.4	2	2.1	1	0.3	1	1.0

Reviewer comment: *The relative risk arthralgia in subjects treated with concomitant amantadine was 1.1 (3.2% in rasagiline subjects with amantadine/3.0% in placebo subjects with amantadine). The equivalent calculation for neck pain showed an increased relative risk of 2.1, although this is based upon a small number of subjects (two versus one).*

5.2.3 Sponsor Flu Syndrome Discussion

For monotherapy subjects (Cohort 1), Teva acknowledged that although there was an increased incidence of arthralgia in the rasagiline 2 mg group (and therefore a possible dose response), arthritis, conjunctivitis and rhinitis occurred with similar incidence in both the 2 mg and placebo groups. The sponsor asserted that this overall lack of a dose-response relationship was not supportive of a causal role for rasagiline. Teva further noted that no subject reported recurrent bouts of flu syndrome (Rasagiline Approvable Safety Update, pg. 75).

For adjunctive therapy subjects (Cohort 2), Teva stated that, as with monotherapy subjects, no patient on adjunct therapy had repeated bouts of flu syndrome. When the sponsor analyzed the adjunctive therapy data by study, they found that in the North-American study (PRESTO) the incidence of flu syndrome for the rasagiline 0.5 mg, 1 mg and placebo groups was 1.2% (2 patients), 1.3% (2 patients), and 0%, respectively. In the non-North American study LARGO, an equal incidence of flu syndrome was observed among treatment groups: 0.9% (2 patients) for the rasagiline 1 mg, entacapone and placebo groups (Rasagiline Safety Update, pg. 75). The sponsor did not comment on this difference between studies, but did state that the low incidence of flu syndrome in adjunct therapy subjects suggests that flu syndrome is not rasagiline-related (Rasagiline Approvable Safety Update, pg. 78).

Teva noted that most patients (5/7 in the 1 mg group, 2/4 in the 2 mg group and 1/1 in the placebo group) in the monotherapy study TEMPO reported flu syndrome during the peak influenza season in the United States (December through March). The sponsor

commented that this suggests a viral etiology for these symptoms (Rasagiline Approvable Safety Update, pg. 75).

Finally, the sponsor noted that the other Parkinson's disease (PD) therapies have also demonstrated an imbalance in flu syndrome or related adverse events between the placebo and treatment groups in double-blind placebo-controlled studies. Specifically, patients treated with ropinirole in early PD had an 11% incidence of viral syndrome versus 3% for placebo, and advanced PD patients treated with pergolide had a 12% incidence of rhinitis versus 5% for placebo, as per labeling found in the 2003 Physician's Desk Reference (Rasagiline Approvable Safety Update, pg. 76).

5.2.4 Sponsor Musculoskeletal Adverse Event Discussion

The sponsor stated that in both cohorts, subjects reporting the adverse event of arthralgia had past or current musculoskeletal conditions. The sponsor qualified that this comparison was limited to those subjects for whom prior medical history was available.

Reviewer comment: *In the above analysis the sponsor did not comment on the following:*

- *The percentage of subjects for whom prior medical history was available*
- *What percentage of subjects not reporting arthralgia also had a prior history of musculoskeletal conditions*
- *Whether subjects with a prior history of musculoskeletal conditions and subsequently reporting arthralgia experienced arthralgia in the same anatomic location (or a related location) as their prior conditions*

For monotherapy (Cohort 1) subjects, as noted previously, arthralgia was the only musculoskeletal adverse event demonstrating a potential dose-response effect; neck pain, joint disorder and arthritis had decreased or similar incidence in the rasagiline 2 mg group compared the 1 mg group. Teva further characterized musculoskeletal adverse events occurring in the cohort by searching for the combined terms arthralgia, arthritis and joint disorder. The sponsor stated, however, that two patients in the 1 mg group, one patient in the 2 mg group and one placebo patient were excluded from this analysis "after review of the data listings indicated that the joint complaints were related to prior or concomitant injury" (Rasagiline Approvable Safety Update, pg. 76).

Reviewer comment: *The sponsor did not provide additional details regarding the excluded subjects. Although it may be appropriate to exclude subjects for whom the musculoskeletal complaints are clearly related to a condition pre-existing rasagiline treatment, it is also possible that rasagiline-precipitated pain in an anatomic site previously affected by another condition could be inappropriately excluded. Given the relatively small number of exclusions and their roughly equivalent distribution across treatment groups, the exclusions would not be expected to impact the overall analysis.*

FDA Table 30: Number of Monotherapy (Cohort 1) Patients with Complaints Related to a Specific Joint (Adapted from Sponsor Post-Text Table 91, Rasagiline Approvable Safety Update, pg. 239)

Pre-Approval Update of Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment	Rasagiline 1 mg (N=149)	Rasagiline 2 mg (N=146)	Placebo (N=151)
Joint Involved	n (%)	n (%)	n (%)
Shoulder	8 (5.4)	3 (2.1)	5 (3.3)
Hip	2 (1.3)	3 (2.1)	0 (0.0)
Knee	2 (1.3)	5 (3.4)	0 (0.0)
Elbow	1 (0.7)	2 (1.4)	0 (0.0)
Wrist	1 (0.7)	1 (0.7)	1 (0.7)
Hand	1 (0.7)	0 (0.0)	0 (0.0)
Not specified	1 (0.7)	0 (0.0)	1 (0.7)
Heel	0 (0.0)	1 (0.7)	0 (0).0
TM joint (mouth)	0 (0.0)	1 (0.7)	0 (0.0)
Spine	0 (0.0)	1 (0.7)	0 (0.0)

The sponsor noted that shoulder and upper extremity complaints predominated in the rasagiline 1 mg and placebo groups, but not in the 2 mg group. Teva reported there was no correlation between neck and shoulder/upper extremity pain in the rasagiline-treated subjects (Rasagiline Approvable Safety Update, pg 240).

For adjunct therapy subjects (Cohort 2), the sponsor stated arthralgia was the only musculoskeletal adverse event showing an increased incidence in the 1 mg group over placebo (Rasagiline Approvable Safety Update, pg. 240).

FDA Table 31: Number of Adjuct Therapy (Cohort 2) Patients with Complaints Related to a Specific Joint (Adapted from Sponsor Post-Text Table 92, Rasagiline Approvable Safety Update, pg. 240)

Pre-Approval Update of Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	Rasagiline 1 mg (N=380)	Placebo (N=388)
Joint Involved	n (%)	n (%)
Shoulder	4 (1.1)	1 (0.3)
Hip	3 (0.8)	2 (0.5)
Knee	3 (0.8)	1 (0.3)
Not specified	1 (0.3)	0 (0.0)

Teva reported that the prominence of shoulder and upper extremity related complaints, seen in the monotherapy cohort, is not observed in the adjunctive therapy cohort.

However, the sponsor noted that of the six rasagiline-treated patients with neck pain, two also experienced the AE of shoulder pain and one had "sore neck and shoulder" coded only as neck pain.

Teva asserted that shoulder pain frequently occurs in Parkinson's disease patients. The sponsor further stated that shoulder pain may be a presenting symptom or a late manifestation, and described several possible underlying mechanisms. Teva noted that falls can lead to fractures and other musculoskeletal injuries that cause joint pain, and that dyskinesia may have played a role in the increased incidence of arthralgia the more advanced PD patients on rasagiline versus placebo in the PRESTO study.

Reviewer comment: *With regards to the sponsor's hypothesis on dyskinesia, it is notable that the LARGO adjunctive study was conducted in subjects with similarly advanced PD, and did not demonstrate the same pattern of shoulder pain.*

Finally, as with flu syndrome, the sponsor noted that the United States labeling for another Parkinson's disease therapy, ropinirole, also noted an increased incidence of arthralgia (7% ropinirole, 5% placebo) and arthritis (3% ropinirole, 1% placebo) with treatment in the double-blind, placebo-controlled advanced PD trials (Rasagiline Approvable Safety Update, pg. 77).

Reviewer comment: *Since all subjects (both placebo and treatment) had PD, the fact that an elevation of risk is observed in the treatment group with another PD therapy may be considered supportive of a role for the drug, perhaps through some shared mechanism for the two therapies. However, as discussed throughout this section, other factors point away from a strong causal relation between drug exposure and a flu or musculoskeletal syndrome.*

5.2.5 Sponsor Overall Conclusions

Teva concluded that there is no readily apparent explanation for the increased incidence of flu syndrome observed in the 1 mg group of early PD patients on rasagiline monotherapy, and to a lesser extent in the 2 mg group. However, as per the discussion above, the sponsor maintained that the data does not support a causal role for rasagiline (Rasagiline Approvable Safety Update, pg. 78). The sponsor stated that despite the multifactorial etiology of shoulder and other joint pains in both monotherapy and adjunctive therapy subjects, the possibility of arthralgia as a drug effect cannot be excluded. However, Teva maintained that there is no evidence in either cohort for a "syndrome" of musculoskeletal AEs and flu-like symptoms associated with rasagiline therapy.

Reviewer comment: *I generally agree that, from the further analysis described above, a discernable pattern demonstrating either the existence of a flu/musculoskeletal syndrome or a causal relation of rasagiline to these adverse events is not apparent. However, if*

rasagiline receives marketing approval in the United States, this issue should be re-visited as additional data, either in further trials or in the post-marketing period, is accumulated.

6. LABORATORY AND VITAL SIGN DATA

6.1 FDA Request in Approvable Letter

> "4a. For the laboratory and vital sign data, please provide an analysis of mean change from baseline to subject's *Maximal* Observed Value for the various parameters.
>
> 4b. For the analysis of Potentially Clinically Significant (PCS) values for both laboratory and vital sign data, please clarify whether all values were evaluated on PCS criteria, or only the LOV. If LOV only, please repeat the laboratory and vital sign analysis evaluating on the PCS criteria." (NDA 21-641, Rasagiline Approvable Letter, pg. 7)

6.2 Sponsor Response

Teva described that the following descriptive statistics for the change from baseline visit to maximal observed value for vital signs and clinical laboratory parameters were calculated as the maximal increase change from baseline (values greater or equal to baseline) and the minimal observed values were calculated as the maximal decrease change from baseline (values smaller or equal to baseline), at any time during the study (Rasagiline Approvable Safety Update, pg. 79).

6.2.1 Clinical Laboratory Analysis to Maximal Observed Value

Teva provided tables summarizing the descriptive statistics for mean change from baseline for maximal increase and decrease for the hematology and chemistry laboratory values. The sponsor stated that no prominent effect of rasagiline on these parameters was observed, which Teva asserted was consistent with the findings of the original ISS[52] for both the monotherapy and adjunctive therapy cohort (Rasagiline Approvable Safety Update, pg. 79).

Reviewer comment: *I reviewed Post-Text Tables 93 to 102, which contained the re-analysis of clinical laboratory data, looking at mean change to maximal increase or decrease from baseline, and verified the sponsor's claim that no significant effect for the parameters was present.*

6.2.2 Vital Sign Analysis to Maximal Observed Value

[52] ISS = Integrated Summary of Safety

For monotherapy subjects (Cohort 1), Teva stated that a slightly larger mean maximal decrease of standing systolic blood pressure (SBP) was noted for the 2 mg dose of rasagiline (16.2 mm Hg) as compared to the 1 mg (14.5 mmHg) and placebo (14.0 mmHg). Mean maximal supine minus standing SBP (i.e., mean maximal postural decrease in SBP) tended to increase from placebo to rasagiline 1 mg and 2 mg (10.9, 12.0 and 13.6 mmHg, respectively) (Rasagiline Approvable Safety Update, pg. 79).

For adjunctive subjects (Cohort 2), the sponsor reported that there was also a slight increase in mean maximal postural change (i.e., supine minus standing SBP and DBP) for rasagiline 1 mg as compared to placebo (11.9 versus 10.5 mmHg for SBP and 8.3 versus 7.4 mmHg for DBP, respectively)(Rasagiline Approvable Safety Update, pg. 79).

6.2.3 Clarification of PCS Analysis

Teva clarified that for PCS (Potentially Clinically Significant) analysis of laboratory and vital sign values in the ISS of the original NDA, values measured at any time during the study (and not just at the last observed value) were evaluated according to PCS pre-defined criteria (Rasagiline Approvable Safety Update, pg. 80). Therefore no additional analyses were submitted.

7. MISSING AE ATTRIBUTION OF DISCONTINUATIONS

7.1 FDA Request in Approvable Letter

> "For approximately 7% of discontinuations in the rasagiline development program, the discontinuation was not attributed to a specific AE. Additional measures should be taken to identify the AE associated with discontinuation for a particular subject. This may include evaluating a listing of all AEs reported by discontinuing subjects along with the dates of their AEs and discontinuation. The frequency table for adverse events leading to discontinuation should be updated with the additional information." (NDA 21-641, Rasagiline Approvable Letter, pg. 7)

7.2 Sponsor Response

7.2.1 AE Attribution Results

Teva summarized that in the 120-Day Safety Update premature discontinuation 'due to AE' was reported for 138 (10.1%) of all patients exposed to rasagiline. Of these 138, 128 patients had a specific AE associated with discontinuation of the study drug. The remaining ten patients (10/138, 7%) were characterized as discontinuing due to an AE, but with no specific AE identified (Rasagiline Approvable Safety Update, pg. 80).

The sponsor stated that further examination of the data for these ten patients revealed the following AEs as the precipitant to the subjects' discontinuations (presented in the table below):

FDA Table 32: Newly Identified AEs Leading to Discontinuation among 10 Rasagiline Development Program Subjects with no AE Identified in the Initial NDA Submission

Subject	**AE Leading to Discontinuation**	**Data Source Sponsor Used to Identify an AE**
1. TVP-1012/123 #16222	Syncope	Safety Database
2. TVP-1012/123 #16414	Rash	Safety Database
3. TVP-1012/123 #80702	Extrapyramidal Syndrome	Safety Database
4. TVP-1012/135 #755	Dizziness	Safety Database
5. TVP-1012/133 #544	Hypertension	Subject Narrative
6. TVP-1012/232 #179	Vascular Disorder	Subject Narrative
7. TVP-1012/133 #169	Melanoma	Subject Narrative
8. TVP-1012/233 #118	Melanoma	Subject Narrative
9. TVP-1012/135 #109	"Omitted from the list"	NA
10. TVP-1012/133 #756	"Omitted from the list"	NA

Study Codes: 123 = Extension of Adjunctive Therapy LARGO, 133 = Adjunctive Therapy Study PRESTO, 135 = Extension of Adjunctive Therapy Study PRESTO, 232 = Monotherapy Study TEMPO, 233 = Extension of Monotherapy Study TEMPO

The final two subjects (TVP-1012/135 #109 and TVP-1012/133 #756) were described as "omitted from the list" in the sponsor's Approvable Letter Safety Update (Section 7.3, pg. 80). The sponsor was contacted (via e-mail) for additional details on these two subjects. Teva responded[53] by clarifying that after further examination it was determined that the patients did not discontinue due to an adverse event and had been inappropriately included in the initial count of subjects discontinuing due to an unspecified AE. Teva provided the following additional information on the circumstances of these two patients:

1. **TVP-1012/135 #109** was withdrawn from the study due to a diagnosis of malignant melanoma in situ made by the local pathology laboratory assessing melanoma surveillance biopsies. The diagnosis of malignant melanoma in situ made by the local laboratory was reassessed as a melanocytic nevus (compound type) by the central laboratory (More details on the re-assessment process is provided below). By the time the central laboratory response was received, the subject had already discontinued the study. Consequently, the sponsor stated that termination reason was downgraded by the investigator from "due to AE" to "patient withdrew consent."

[53] E-mail communication from Teva received February 18, 2005.

Reviewer comment: *Additional discussion of discrepancies in the central versus local laboratory readings of melanomas and its potential impact on melanoma ascertainment is provided in Section 2.4 of this review.*

2. **TVP-1012/133 #756** underwent a biopsy from a pigmented lesion on screening skin exam. The subject was randomized to receive 0.5 mg rasagiline two days later, before the results of the biopsy were obtained. He withdrew from the study due to malignant melanoma in situ after 20 days in the study. The sponsor explained that this case was not added to the listings and table of discontinuation due to AE because the cause for discontinuation was condition which pre-existed rasagiline treatment.

7.2.2 Comparison of Most Common AEs Before and After Additional AE Attribution

The sponsor presented the following revised AE table with the ten subjects with newly attributed AEs included.

FDA Table 33: Adverse Events Resulting in Early Discontinuation by COSTART Term and Descending Order of Incidence (Adapted from Sponsor Table 48, Rasagiline Approvable Safety Update, pg. 81)

Table 48. Cohort No. 9: Frequency and Incidence of Adverse Events Resulting in Early Discontinuation by COSTART Term and Descending Order of the Incidence*

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)			
	No. of Reports	No. of Reports Per 100 Patient Years	No. of Patients	% of Patients
HALLUCINATIONS	21	0.9	18	1.3
HYPERTENSION	10	0.4	10	0.7
SKIN MELANOMA	12	0.5	10	0.7
NAUSEA	9	0.4	9	0.7
DIZZINESS	9	0.4	9	0.7
POSTURAL HYPOTENSION	7	0.3	7	0.5
FALL	8	0.3	7	0.5
EXTRAPYRAMIDAL SYNDROME	7	0.3	7	0.5
PSYCHOSIS	8	0.3	7	0.5
ASTHENIA	8	0.3	6	0.4

*Ten most common AEs that resulted in early discontinuation

For comparison, the corresponding table with data from the 120 Day Safety Update (without the newly attributed ten cases) is provided below. It should be noted that the change in the number of subjects per adverse event includes both the addition of the eight newly classified adverse events and the accumulation of additional adverse events and person-years as the trials continued over time.

FDA Table 34: Ten Most Common Adverse Events Resulting in Early Discontinuation by COSTART Term and Descending Order of Incidence from the 120 Day Safety Update (Adapted from 120 Day Update Post-Text Table 47)

120 Day Update of the ISS Cohort No. 9: All PD Patients Ever Exposed to Rasagiline	**Original NDA Safety Database Rasagiline (N=1360)**		
	No. of Reports	**No. of Patients**	**% of Patients**
HALLUCINATIONS	16	14	1.0
HYPERTENSION	9	9	0.7
NAUSEA	9	9	0.7
DIZZINESS	8	8	0.6
ACCIDENTAL INJURY	7	7	0.5
POSTURAL HYPOTENSION	7	7	0.5
SKIN MELANOMA	8	6	0.4
DEPRESSION	6	6	0.4
ASTHENIA	5	4	0.3
PSYCHOSIS	5	4	0.3

Reviewer comment: *The subsequent attribution of the ten cases of discontinuation due to unspecified adverse event did not substantially change the frequency of adverse events as presented in the 120 Day Safety Update.*

8. RHABDOMYOLYSIS

8.1 FDA Request in Approvable Letter

> "The two cases of rhabdomyolysis occurring during the rasagiline development program both followed a fall and prolonged immobilization, and one lacked laboratory (CPK) confirmation. These two cases do not appear to represent a significant safety signal, but close monitoring in the postmarketing period is recommended, and it is requested that 15-day reports be submitted for any cases of CPK increased, myalgia, myopathy, rhabdomyolysis, and related adverse events in the postmarketing period." (NDA 21-641, Rasagiline Approvable Letter, pg. 7)

8.2 Sponsor Response to Question

Teva proposed the following criteria for postmarketing 15-day "alert reports" in cases of suspected myopathy or rhabdomyolysis (Rasagiline Approvable Letter Response: Rhabdomyolysis, pg. 2):

1. Ten-fold elevation of CPK[54] concentration from baseline levels as a sole criterion[55]
2. Elevated CPK values (irrespective of the level) accompanied or not by myalgia with combination of *one or more* of the following:
    a. Acute or acute on chronic renal failure
    b. Hyperkalemia
    c. Metabolic Acidosis
    d. Hypocalemia
    e. Hypercalemia
    f. Recent elevation of uric acid from a baseline value
3. Any other case which was assessed by the reporter or company's medical reviewer as suggestive of myopathy or rhabdomyolysis.

The sponsor cited the following as a basis for these criteria:

1. Teva asserted that Parkinson's disease patients in general have been demonstrated to exhibit higher CPK levels (almost twice the gender- and age-control matched values)[56], and symptoms such as myalgia and muscle weakness are common in this population. The sponsor stated that based upon these observations they believed that one should anticipate a substantial number of confounded reports with respect to suspected rhabdomyolysis cases in the PD population. Teva therefore maintained that there is a need to determine in advance a category of symptoms, signs and laboratory values which will be broad enough to capture all suspicious cases of rhabdomyolysis or myopathy, which might progress to rhabdomyolysis, without introducing the confounding effect of features of the basic disease.

2. Teva stated that it is noteworthy that there is no single uniformly accepted definition of rhabdomyolysis, nor a threshold of CPK values defining the condition. Teva asserted that the reason for this stems from the fact patients with less severe symptoms may not seek immediate medical attention. The sponsor noted that because CPK has a relatively short half-life (24 hours), a patient with myalgia of a week's duration and current CPK values of 800 IU/L could represent a case with an initial CPK concentration of over 100,000 IU/L a week earlier.

[54] CPK = Creatinine Phosokinase
[55] Sponsor-identified reference: Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother. 2002;36(2):288-295.
[56] Sponsor-identified reference: Takubo H, Shimoda-Matsubayashi S, Mizuno Y. Serum creatinine kinase is elevated in patient with Parkinson's disease: a case controlled study. Parkinsonism Related Disorders 2003;9 Suppl 1:S43-S46.

Reviewer comment: *From a brief review of the literature and referral to prior DNDP evaluations of rhabdomyolysis, I would agree that there are no widely agreed upon criteria for the identification of rhabdomyolysis cases. The sponsor-proposed criteria above are generally acceptable with the following exception: the criteria of a 10-fold elevation of CPK should be reduced to a 5-fold elevation. I reviewed the article referenced by the sponsor for this criterion, which defined myopathy with statin usage as a 10-fold CPK elevation. However, as noted by the sponsor above, due to the short half-life of CPK if the measurement is not made promptly even a 5-fold elevation could represent significant previous myopathic injury. It is recognized that by lowering this threshold some cases of CPK elevation that do not represent rhabdomyolysis may be captured. However, given that postmarketing cases are likely already reduced due to under-reporting, it is preferable not to lose additional cases due to screening criteria with insufficient sensitivity.*

9. ANTIDEPRESSANT USE AND SEROTONIN SYNDROME

9.1 Introduction

9.1.1 Review Content

This review addresses a subsection of Teva's November 2004 response to the approvable letter examining the concomitant use of antidepressants and rasagiline (an MAO inhibitor) with regards to serotonin syndrome. Although this issue was not included as a specific question to the sponsor within the rasagiline Approvable Action letter, DNDP had added language to the Warnings section of the labeling proposal included with the Approvable letter addressing the potential risks associated with concomitant use of rasagiline and antidepressants (based on similar labeling in the selegiline package insert).

9.1.2 Serotonin Syndrome: General Information

The sponsor noted that current labeling for various antidepressant drugs[57] include cautions and/or contraindications to concomitant use of MAO inhibitors (MAOI) due to the risk of serotonin syndrome. Serotonin syndrome results from acutely elevated levels of central serotonin. Onset is generally within 24 hours of administration of the precipitating agent or agents. Diagnostic criteria for serotonin syndrome are generally held to be the combination of any four the following major symptoms, or three major symptoms plus two minor ones (Teva Antidepressant Report, pg. 7).

FDA Table 35: Major and Minor Diagnostic Symptoms of Serotonin Syndrome*

Major Symptoms	Minor Symptoms

[57] These antidepressants include tricyclics (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenalin reuptake inhibitors (SNRIs) and trazodone.

Confusion, Elevated mood, Coma or Semicoma, Fever, Hyperhidrosis, Myoclonus, Tremor, Chills, Rigidity, Hyperreflexia	Agitation and Nervousness, Insomnia, Tachycardia, Tachypnea and Dyspnea, Diarrhea, Low or High Blood Pressure, Impaired Coordination, Mydriasis, Akathisia

*For purposes of serotonin syndrome diagnosis, these symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotenergic agent. Infectious, metabolic, endocrine or toxic causes must also be excluded (Teva references Birmes et al., 2003).

Teva presented introductory information on serotonin syndrome relating to MAOI pharmacologic action. The sponsor states that MAOIs are assumed to contribute to the hyperserotonergic condition by preventing the metabolism of serotonin. Serotonin is held to be a preferential substrate of MAO-A, but can still be metabolized by MAO-B[58]. Teva therefore notes that the interaction can occur with nonselective (irreversible and reversible) and selective MAOIs (Teva Antidepressant Report, pg.7).

Teva stated that another selective inhibitor of MAO-B, selegiline, may also have diminished selectivity problems at high doses. Teva acknowledged that there been reports of serotonin syndrome cases with concomitant use of selegiline and antidepressants, such as SSRIs and TCAs. The sponsor maintains that the observed occurrence of serotonin syndrome in PD patients receiving selegiline is an infrequent event, however. In support of this assertion Teva cited a survey[59] of investigators in the Parkinson Study Group, in which the frequency of "possible serotonin syndrome" among 4,568 patients treated with selegiline and an antidepressant medication was reported as 0.24%, and the frequency of "serious" symptoms was 0.04% (Teva Antidepressant Report, pg. 8).

Reviewer comment: *I conducted a literature search[60] for studies and case reports of serotonin syndrome in patients treated with selegiline. Although the number of case reports was not extensive and it is impossible to estimates rates from such reports, it is noteworthy that fatal cases (with fluoxetine usage) have been observed.[61]*

Teva asserted that because of rasagiline's selectivity for MAO-B as compared to MAO-A, at the recommended therapeutic dose of 1 mg/day rasagiline will induce "significant" inhibition of MAO-B only, and that the risk of serotonin syndrome is therefore unlikely.

Reviewer comment*: Teva did not elaborate on or quantify what was meant by "significant inhibition of MAO-B."*

[58] Rasagiline is a selective inhibitor of the B form of the MAO enzyme.
[59] Richard et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. Neurology 1997. Apr; 48(4):1070-7.
[60] PubMed search for the key words "eldepryl" and "serotonin syndrome" conducted on June 28, 2005.
[61] Bilbao et al. Serotonin syndrome: report of a fatal case and review of the literature. Rev Clin Esp. 2002 Apr;202(4):209-11.

Teva noted that in the case of selegiline, it has been argued that non-specific MAO inhibition may not be the sole contributing factor in the development of serotonin syndrome. The sponsor asserted that selegiline's major metabolite L-methamphetamine can effectively block the cytoplasmic serotonin transporter, thus contributing to a hyperserotonergic condition, whereas rasagiline's major metabolite, 1-aminoindan, lacks this reuptake blocking property. In support of this the sponsor referenced studies in rats, in which the concomitant use of fluoxetine and selegiline, but not of fluoxetine and rasagiline, aggravated the signs of the corresponding rodent syndrome, at similar levels of MAO inhibition, and at even lower of MAO inhibition by selegiline in one study (Finberg, 2002; Speiser, 2003, internal report)(Teva Antidepressant Report, pg. 8).

Reviewer comment: *The DNDP toxicologist assigned to rasagiline, Dr. Paul Roney, was asked to review the internal report referenced by the sponsor regarding differences in the interactions of fluoxetine with rasagiline or selegiline in rodents. Upon an initial review, Dr. Roney indicated*[62] *that the report did not provide strong evidence of a difference in response to the combination of rasagiline or selegiline with fluoxetine, noting that there were deaths in both treatment groups at higher doses and it was unclear whether the sponsor researchers were blinded to treatment.*

9.2 Antidepressant Exposure in the Rasagiline Development Program

9.2.1 Protocol-Allowed Exposure

The following antidepressants and doses allowed in the rasagiline trials, compared with the therapeutic dose range described in the respective antidepressant labeling, are summarized in the following table:

FDA Table 36: Antidepressant Doses Allowed by Protocol in the Rasagiline Development Program

Antidepressant Name	Dose Allowed by Rasagiline Development Program	Therapeutic Dose Range as Per Drug Labeling
Amitriptyline (Elavil ®)	50 mg/daily	25 – 300 mg/day
Trazodone (Desyrel ®)	100 mg/daily	150 – 400 mg/day*
Citalopram (Celexa ®)	20 mg/daily	20 – 60 mg/day**
Sertraline (Zoloft ®)	100 mg/daily	25 – 200 mg/day***
Paroxetine (Paxil ®)	30 mg/daily	20 – 50 mg/day

*The 2003 trazodone labeling states doses up to 600 mg/day may be given to persons receiving the medication in an inpatient setting.
**The citalopram labeling notes that although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for

[62] Personal communication on July 20, 2005.

the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.
*** The 200 mg/day dosing of sertraline is indicated for panic disorder, posttraumatic stress disorder and social anxiety disorder, but not major depressive disorder.

Teva reported that other antidepressants were also administered by investigators, but that concomitant use of fluoxetine (Prozac ®) or fluvoxamine (Luvox ®) with rasagiline was not allowed (Teva Antidepressant Report, pg. 9).

Reviewer comment: The doses of antidepressants allowed by protocol to subjects in the rasagiline development program are considerably lower than the therapeutic range described in the product labeling, and likely even lower still than actual usage within clinical practice. Furthermore, concomitant administration of the widely used antidepressant fluoxetine as well as fluvoxamine were not allowed within the rasagiline development program, so no data was collected on the concomitant use of these drugs. These represent very significant limitations to the data collected within the rasagiline development program, and should be made clear within the rasagiline labeling.

9.2.2 Number Exposed

Teva stated that general cautions regarding the use of anti-depressants and MAOIs notwithstanding, 275 (20.2%) of the 1361 subjects representing all PD patients ever exposed to rasagiline were treated concomitantly with antidepressants of various classes (Teva Antidepressant Report, pg. 9).

FDA Table 37: Percent and Person-Year Exposure to Classes of Antidepressant (Adapted from Sponsor Table 1, Response to Approvable Letter: Antidepressants, pg. 9)

Pre-Approval Update of Rasagiline ISS	Rasagiline			
	PRESTO + TEMPO(N=579)		Cohort No. 9 (N=1361)	
	Concomitant Use of Antidepressants		Concomitant Use of Antidepressants	
	No. of Patients	Total Years of Exposure	No. of Patients	Total Years of Exposure
All Antidepressants	97 (16.8%)	36.9	275 (20.2%)	349.2
SSRIs	52 (9.0%)	20.3	141 (10.4%)	161.3
Tricyclic	35 (6.0%)	12.4	115 (8.4%)	138.5

Reviewer comment: *Teva did not specify how total years of antidepressant exposure was measured and updated within the development program (i.e. from study start, from time of last study visit in which antidepressant use was reported, or from patient-reported dates of treatment initiation and cessation). These possible methods have varying degrees of uncertainty associated with their use.*

Teva stated that the large majority of patients in Cohort 9 (all PD subjects exposed to rasagiline) were treated with amitriptyline (n=106, 7.8%), sertraline (n=69, 5.1%), paroxetine (n=59, 4.3%) and trazodone (n=45, 3.3%). The number of subjects exposed to other specific antidepressants is summarized in the table below.

FDA Table 38: Concomitant Use of Antidepressants by Drug Group and Generic Name for Cohort 9 (All PD Patients Exposed to Rasagiline) (Adapted from Sponsor Post-Text Table 1, Response to Approvable Letter: Antidepressants, pg. 24)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline		Rasagiline (N=1361)	
		N	%
- ALL	- ALL	275	20.2
OTHER ANTIDEPRESSANTS	- ALL	61	4.5
	BUPROPION HYDROCHLORIDE	5	0.4
	MIANSERIN HYDROCHLORIDE	2	0.1
	MIRTAZAPINE	13	1.0
	NEFAZODONE HYDROCHLORIDE	2	0.1
	TRAZODONE HYDROCHLORIDE	45	3.3
SSRI	- ALL	141	10.4
	CITALOPRAM HYDROBROMIDE	26	1.9
	ESCITALOPRAM	6	0.4
	FLUOXETINE HYDROCHLORIDE	7	0.5
	FLUVOXAMINE MALEATE	2	0.1
	PAROXETINE HYDROCHLORIDE	59	4.3
	SERTRALINE HYDROCHLORIDE	69	5.1
	VENLAFAXINE HYDROCHLORIDE	2	0.1
TRICYCLIC	- ALL	115	8.4
	AMITRIPTYLINE	106	7.8
	CLOMIPRAMINE HYDROCHLORIDE	4	0.3
	DOXEPIN HYDROCHLORIDE	1	0.1
	NORTRIPTYLINE HYDROCHLORIDE	5	0.4

Reviewer comment: *As demonstrated in the preceding table, the number of subjects receiving any specific antidepressant concomitantly is relatively small, and in a number of cases is in the single digits (for example bupropion [n=5], escitalopram [n=6], and venlafaxine [n=2].) It also appears that despite being contraindicated by the study protocol a small number of subjects did receive concomitant fluoxetine (n=7) and fluvoxamine (n=2).*

9.2.3 Duration of Exposure

Teva stated that exposure duration to the various antidepressants during the period of co-administration with rasagiline varied from a few days to 6.2 years. The 275 (20.2%) of patients receiving antidepressants in Cohort 9 (all PD patients ever exposed to rasagiline) were treated concomitantly for a total of 349.2 patient-years (Teva Antidepressant Report, pg. 9).

FDA Table 39: Descriptive Statistics of Exposure to Antidepressants by Drug Group for All PD Subjects Exposed to Rasagiline (Cohort 9)(Adapted from Sponsor Table 2, Response to Approvable Letter: Antidepressants, pg. 10)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Rasagiline (N=1361) Duration on Drug (years)						
	N	Mean	SD	Median	Min	Max	Total
Drug Group							
ALL	275	1.3	1.4	0.8	0.003	6.2	349.2
OTHER ANTIDEPRESSANTS	61	1.1	1.5	0.5	0.003	5.8	66.2
SSRI	141	1.1	1.0	1.0	0.003	5.2	161.3
TRICYCLIC	115	1.2	1.5	0.7	0.005	6.2	138.5

By study, in TEMPO (North American monotherapy) 11.3% (n=30) of patients with early PD were taking concomitant rasagiline and antidepressant. In PRESTO (North American Levodopa Adjunct Study), 21.4% (n=67) were treated concomitantly. Teva noted that the incidence of antidepressant use in the combined placebo-controlled, rasagiline cohort (TEMPO+PRESTO) is similar to that of Cohort 9[63], although the extent of exposure is substantially higher in the latter (Teva Antidepressant Report, pg. 10).

Reviewer comment: *See Section 9.3 (Sponsor Analysis) for reviewer comment on the lack of data from the LARGO pivotal study within this sponsor report.*

9.2.4 Exposure by Rasagiline Dosage

Teva noted that 53 of the 275 patients (19.3%) took antidepressants while on the higher rasagiline dose, 2 mg/day. However, Teva commented that some of the patients who were treated initially with 1 or 2 mg/day rasagiline in the TEMPO study switched to 2 mg upon entering the open-extension (TVP-1012/233) and that later in this extension study all patients were changed to rasagiline 1 mg/day (Teva Antidepressant Report, pg. 9).

Reviewer comment: *A follow-up question has been sent to Teva to quantify the "some" of subjects who fell into the 2 mg category, but in fact had received other lower doses for some time period both before and after. In addition, Teva only describes the number of subjects receiving the 2 mg/day dose in their report, and has been asked to specify what percent of the remaining subjects received the 0.5 mg and the recommended 1 mg per day.*

9.2.5 Baseline Characteristics of Subjects Exposed to Antidepressants

When compared to the approximately 1:2 ratio of females to males in Cohort 9 (all PD subjects exposed to rasagiline), the sponsor stated that a slightly higher percentage of females received antidepressants (43.6% of females, 56.4% of males). Otherwise, Teva reported that there were no prominent differences between subjects with regards to age and PD duration at baseline (Teva Antidepressant Report, pg. 9).

[63] Cohort 9 consisted of all PD patients exposed to rasagiline

The sponsor reported that, not unexpectedly, patients (both rasagiline and placebo) who used antidepressants during the study had more severe depression at study entry as assessed by the BECK depression and UPDRS[64] scores.

***Reviewer comment**: Based on Sponsor Post-Text Tables 10, 11 and 12, I confirmed that there were no large differences in baseline characteristics between subjects receiving and not receiving antidepressants.*

Teva stated that the percent of patients using dopamine agonists concomitantly with rasagiline was higher in the antidepressants group (70% versus 56%, respectively). The sponsor stated that levodopa use was comparable between the group at about 70% each (Teva Antidepressant Report, pg. 11).

***Reviewer comment:** Of note, dopamine agonists have been known to influence serotonin levels and affect serotonin syndrome development.[65]*

9.3 Sponsor Analysis

Teva stated that since relatively few patients were enrolled in studies other than TEMPO, LARGO and PRESTO, the analysis of the patients' PD status at study entry was performed only for these studies (Teva Antidepressant Report, pg. 11). The sponsor presented data on the following data within their report:

- Search for serotonin syndrome cases
- Deaths
- Serious adverse events
- Overall adverse events
- Discontinuations due to adverse events

***Reviewer comment:** Although Teva stated that analysis was performed using data from the three pivotal studies (TEMPO, PRESTO and LARGO), in the body of the report only data from the North American studies TEMPO and PRESTO is presented. It is unclear why data from LARGO appears only in Post-Text Table 17 describing baseline characteristics for subjects receiving and not receiving rasagiline, and this will be clarified with the sponsor. However, much of the adverse event data is presented for Cohort 9 (all PD patients exposed to rasagiline within the development program), which would include LARGO subjects.*

In addition, as with prior analyses one must consider whether it is appropriate to combine data from TEMPO and PRESTO. Although both studies utilized North American patients, TEMPO was a study of rasagiline monotherapy in early PD patients and PRESTO was a levodopa adjunct study in subjects with more advanced PD. Indeed,

[64] UPDRS = Unified Parkinson Disease Rating Scale
[65] Sandyk R. L-dopa induced "serotonin syndrome" in a parkinsonian patient on bromocriptine. J Clin Psychopharmacol 1986. Jun(3):194-5.

use of antidepressants was twice as high in PRESTO (21%) than in TEMPO (11%)[66]*, presumably reflective of underlying differences in the two study populations.*

9.3.1 Serotonin Syndrome Cases

9.3.1.1 Serotonin Syndrome Cases: Sponsor Search Criteria

Teva reviewed the AEs of 275 rasagiline-treated patients in Cohort 9 (all PD subjects exposed to rasagiline) who received concomitant antidepressants in order to identify any signs/symptoms that may be associated with serotonin syndrome. The sponsor stated they utilized even broader diagnostic criteria than those described in Section 9.1.2, and conducted a search for any subject experiencing two or more of the major adverse events, or one major and two or more minor events. Teva stated that patients were "flagged" if any combination of these serotonin syndrome associated AEs occurred within 48 hours of each other (Teva Antidepressant Report, pg. 11).

9.3.1.2 Serotonin Syndrome Cases: Sponsor Search Results

Teva stated that no patients met their search criteria for serotonin syndrome cases. The sponsor did note one patient (TVP-1012/233 #245) on rasagiline and an antidepressant (not specified by the sponsor) who experienced one major and two minor symptoms: tremor, agitation, and sleep disorder/insomnia. Teva reported that although the tremor and agitation began concomitantly, the insomnia began four days later and thus did not fully meet the case criteria (Teva Antidepressant Report, pg. 12).

Reviewer comment: *I reviewed the discontinuation narrative within the TEMPO extension study report for the subject meeting some but not all of the sponsor's search criteria (TVP-1012/233 #245). The narrative stated that during a hospitalization for suicidal ideation the subject was treated with mirtazapine, although it was unclear if the subject received this or another antidepressant before and subsequent to this admission. In addition, the subject was noted to have diarrhea, one of the potential minor symptoms associated with serotonin syndrome. It is not clear why this was not noted in the sponsor report, although the narrative does describe the diarrhea as chronic, and from the narrative wording it may have preceded study entry.*

9.3.2 Deaths

Teva stated that one death occurred in a patient treated with rasagiline and the antidepressant medications amitriptyline and paroxetine (Teva Antidepressant Report, pg. 16):

> **TVP-1012/233 #287:** This 79 year old female with Parkinson's disease had a history of hypertension, cardiomyopathy, angina, esophageal reflux disease, hypothyroidism,

[66] Teva Antidepressant Report, pg. 10.

arthritis, anxiety, depression, hypercholesterolemia and urinary incontinence. She was treated with rasagiline for 5.9 years. She presented with acute metabolic acidosis and renal failure secondary to ischemic bowel, refused surgical intervention and subsequently died.

Reviewer comment: *The sponsor's report did not note the length of time the subject was treated concomitantly with rasagiline and the antidepressant medications, or whether she was still receiving the antidepressants in the period prior to her death. However, as per the summary above and the more detailed narrative[67], this death does not appear to have the hallmarks of serotonin syndrome, even though serotonin syndrome may occasionally present with renal failure resulting from myoclonus/rhabdomyolysis[68].*

9.3.3 Serious Adverse Events

Teva displayed the top ten SAEs by descending order of the difference in the frequency between comparator groups for all antidepressant-treated patients.

FDA Table 40: Time-Adjusted Frequency of Serious Adverse Events by Descending Order of Difference* Between Concomitant Use Versus No Use of All Antidepressants for Cohort 9 (All PD Patients Exposed to Rasagiline)(Adapted from Sponsor Table 7, Teva Antidepressant Report, pg. 17)

-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Concomitant use of Antidepressants		USE vs. NO USE
	YES (N=275, Patient-Years=349.2)	NO (N=1086, Patient-Years=1767.5)	
	No. of Reports Per 100 Patient Years	No. of Reports Per 100 Patient Years	
SYNCOPE	2.6	0.6	2.0
JOINT DISORDER	2.0	0.7	1.3
DEPRESSION	1.4	0.1	1.3
NEUROPATHY	1.1	0.1	1.1
HEART FAILURE	1.1	0.2	0.9
INFECTION	1.1	0.4	0.7
ANURIA	0.6	.	0.6
ANXIETY	0.6	.	0.6
ATRIAL FLUTTER	0.6	.	0.6
WEIGHT LOSS	0.6	.	0.6
SKIN CARCINOMA	.	0.5	-0.5
GASTROINTESTINAL HEMORRHAGE	.	0.5	-0.5
MYOCARDIAL INFARCT	.	0.5	-0.5
CORONARY ARTERY DISORDER	.	0.7	-0.7
SKIN MELANOMA	0.3	1.1	-0.8

*Ten SAEs with the greatest difference in time-adjusted frequency of Use over No Use and at least -0.5 reports/100 patient-years in No Use over Use

[67] Death narrative in sponsor Appendix 6.4.
[68] Bilbao et al. Serotonin syndrome: report of a fatal case and review of the literature. Rev Clin Esp. 2002 Apr;202(4):209-11.

Reviewer comment: *Teva presented adverse events data within the body of the report as absolute change in events per person-time. The sponsor Post-Text Tables provided the percent of subjects affected by a particular adverse event for rasagiline-treated subjects receiving or not receiving antidepressants, but does not provide the equivalent information for placebo subjects, as this is not included in Cohort 9 (all PD patients exposed to rasagiline). It is therefore not possible to calculate relative risk of an adverse event with the data provided (i.e. percent in rasagiline subjects* ***with*** *antidepressants/percent in placebo subjects* ***with*** *antidepressants compare with percent in rasagiline subjects* ***without*** *antidepressants/percent in placebo subjects* ***without*** *antidepressants).*

Teva offered the following commentary on the AEs with the highest difference in frequency between the antidepressant treated and untreated groups.

Syncope: The sponsor reported that syncope was observed in four patients receiving SSRIs. Teva noted the following about the four cases (Teva Antidepressant Report, pg. 17):

- All four cases were associated with postural hypotension.
- TVP-1012/123 #50510 had received fluvoxamine for several weeks, which Teva noted was a disallowed medication.
- TVP-1012/233 #212, receiving mirtazapine, had a prior history of postural hypotension and experienced syncope associated with dehydration.
- TVP-1012/233 #287 received both amitriptyline and paroxetine for a number of years while on the study drug. She had a syncopal episode while taking amitriptyline alone (and rasagiline 2 mg) leading to a fall. Teva stated that the resulting musculoskeletal injuries were each coded as a separate SAE of syncope for the same date, for total of four SAEs, which may have contributed somewhat to the high time-adjusted frequency for syncope.

Infection: Teva stated that infection was reported in two patients receiving TCAs (TVP-1012/133 #425 with infective bursitis , TVP-1012/135 #605 with pneumonia/empyema) one patient receiving SSRI (TVP-1012/233 #609 with empyema), and one patient on both SSRI and TCA (TVP-1012/233 #287 with post-surgical knee infection)(Teva Antidepressant Report, pg. 18).

Teva also provided separate tables[69], similar to Table 40 above, for serious adverse events among the subsets of subjects taking SSRIs or TCAs. The sponsor noted that syncope, depression and infection were common to all three tables. Teva stated that certain SAEs seem to be more prominently associated with either SSRI or TCA treatment.

Specifically, for SSRI treatment, Teva commented on the following adverse events (Teva Antidepressant Report, pg. 18):

[69] Sponsor Table 8 (pg. 19) and Table 9 (pg. 20), Teva Antidepressant Report.

- *Accidental Injury:* All five antidepressant subjects with the AE of accidental injury were receiving SSRIs, although one was receiving both amitriptyline and sertraline. Teva noted that except for one motor vehicle accident, the other injuries were all related to falls. Teva stressed that postural hypotension has been observed during the clinical development and postmarketing of some SSRIs (paroxetine and citalopram).
- *Neuropathy:* Two subjects receiving rasagiline and SSRIs reported various neuropathies.
- *Psychosis:* Two subjects receiving rasagiline and SSRIs experienced psychosis, although in both cases there were recent changes in other suspect medications (benzodiazepine withdrawal, amantadine treatment, and ropinirole titration.)
- *Joint Disorder:* Teva stated that all except one of the reports of joint disorder or arthritis with concomitant SSRI use was associated with elective spinal surgery or joint replacement.
- *Atrial Fibrillation*: One subject receiving rasagiline 2 mg and paroxetine experienced three episodes of atrial fibrillation.

For TCA treatment, Teva noted the following adverse events (Teva Antidepressant Report, pg. 19):

- *Cardiovascular Events:* TCAs had a higher frequency of cardiovascular SAEs including heart failure (three patients) and supraventricular tachycardia/atrial flutter (one patient). A cerebrovascular accident was reported in two subjects receiving concomitant amitriptyline.
- *Anemia:* One subject with esophagitis experienced two episodes of anemia.

Reviewer comment: *With the caveats that the sponsor data is based upon small numbers, restricted doses and lack of a placebo comparison group, the above does not demonstrate a significant pattern of SAEs associated with concomitant rasagiline and antidepressants that would not be expected with use of either medication alone.*

9.3.4 Overall Adverse Events

9.3.4.1 Overall Adverse Events: All Antidepressants

Teva stated that the risk (percent) of adverse events was similar for patients taking and not taking antidepressants. However, the overall time-adjusted frequency of adverse events was higher in the group taking antidepressants (557 versus 446 reports/100 patient-years). The table below summarizes the top ten AEs in descending order of the difference in the number of reports (time-adjusted) in the group taking any concomitant antidepressant versus those not taking them (Teva Antidepressant Report, pg. 12).

FDA Table 41: Time-Adjusted-Frequency of Adverse Events by COSTART Term and Descending Order of the Difference* of Concomitant Use Versus No Use of All

Antidepressants for Cohort 9 (All PD Subjects Exposed to Rasagiline)(Adapted from Sponsor Table 4, Teva Antidepressant Report, pg. 13)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Concomitant use of Antidepressants		USE vs. NO USE
	YES (N=275, Patient-Years=349.2)	NO (N=1086, Patient-Years=1767.5)	
	No. of Reports Per 100 Patient Years	No. of Reports Per 100 Patient Years	
DEPRESSION	17.5	3.2	14.2
SLEEP DISORDER	14.6	8.0	6.6
FALL	18.3	11.9	6.4
ANXIETY	8.3	2.7	5.6
DYSKINESIA	14.0	9.3	4.7
JOINT DISORDER	7.4	3.3	4.1
ARTHRITIS	6.3	2.7	3.6
TENDON DISORDER	4.3	0.9	3.4
RASH	8.0	5.1	2.9
PAIN	12.9	10.0	2.9
HYPERGLYCEMIA	0.6	1.6	-1.1
CORONARY ARTERY DISORDER	.	1.1	-1.1
MIGRAINE	.	1.2	-1.2
NECK PAIN	1.7	2.9	-1.2
DIZZINESS	12.3	13.7	-1.4
SKIN BENIGN NEOPLASM	4.6	6.1	-1.5
TREMOR	1.4	3.2	-1.8
LEG CRAMPS	1.1	3.0	-1.9
SKIN CARCINOMA	5.7	8.3	-2.6
MYALGIA	1.4	4.4	-2.9
HEADACHE	9.5	15.0	-5.6

*Ten AEs with the greatest *absolute* difference in time-adjusted frequency of 'Use over No Use' and in 'No Use over Use'

The sponsor offered the following commentary on the adverse events in the preceding table with the largest differences between patients receiving and not receiving antidepressants. Teva noted that the higher rate of depression in persons taking antidepressants is not surprising. The sponsor additionally hypothesized that the higher rate of sleep disorder and anxiety may also be manifestations of depressive disorders.

Teva stated that the other frequently reported nervous system AE that was higher in the antidepressant treatment group was dyskinesia, although the sponsor noted that the rate in the two groups was similar (12% antidepressant group versus 10.5% non-antidepressant group). The sponsor speculated that this relative excess of dyskinesia in patients receiving antidepressants could be a manifestation of anti-PD treatment in patients with progression of PD (Teva speculated that increasing dyskinesia could worsen depression). However, Teva also stated that extrapyramidal syndrome/dyskinesia has been reported with amitriptyline use (Teva Antidepressant Report, pg. 12).

Teva considered the increased rate of falls in the antidepressant group to be multifactorial. The sponsor stated that there is, overall, a slight increase in frequency and incidence of postural hypotension (9.1% antidepressant versus 8.1% non-

antidepressant)[70] and syncope (3.6% versus 2.7%) in the antidepressant-treated group, but no overall tendency to arrhythmia. As noted in Section 9.3.4.3 below, Teva stated that postural hypotension and/or hypotension were frequent AEs during the clinical development program and/or post-marketing experience of various antidepressants. Regarding other possible contributors to falls, Teva noted that the musculoskeletal AEs of joint disorder, arthritis and tendon disorder were reported more frequently in antidepressant-treated patients, but the musculoskeletal AEs of myalgia, leg cramps and neck pain were among the most frequently reported AEs in the non-antidepressant-treated group compared to patients on antidepressant. The sponsor further noted that although the antidepressant-treated group had a higher time-adjusted frequency for falls, the difference in incidence between the two groups is less than 2% (13.5% versus 11.7%)(Teva Antidepressant Report, pg. 13).

9.3.4.2 Overall Adverse Events: SSRIs

Teva began their discussion by listing adverse events they considered to be associated with SSRI treatment alone, as per various sources[71]. These included (Teva Antidepressant Report, pg 14):

- Teva noted that the product labeling for the most frequently used SSRIs in the rasagiline clinical program lists the following as treatment emergent AEs for at least two of these three (Paxil® [paroxetine], Zoloft ® [sertraline] and Celexa ® [citalopram]) drugs: asthenia/fatigue, anorexia, abdominal pain, nausea, diarrhea, dry mouth, somnolence, insomnia, dizziness, sexual dysfunction (male and female), increased sweating, agitation, pain, abnormal vision, yawning and rhinitis.
- Adverse events leading to discontinuation within the labeling for at least two of these three drugs included asthenia, nausea, dry mouth, somnolence, insomnia, dizziness and agitation.

Teva noted that when analyzed by descending order of absolute time-adjusted frequency of use over no use of SSRIs[72], urinary tract infection, accidental injury, back pain and skin disorder were not part of the top ten list of overall antidepressant use over no use (Table 4). Similarly, cataract, pharyngitis and eye disorder are newly noted for no SSRI use over use.

9.3.4.3 Overall Adverse Events: Tricyclics

[70] Teva Post-Text Table 19
[71] Teva stated that these adverse events were from the sections of labeling describing short term placebo-controlled studies
[72] Sponsor Table 5, Teva Antidepressant Report, pg. 14.

Teva began their discussion by listing adverse events they considered to be associated with TCA treatment alone, as per various sources[73]. These included (Teva Antidepressant Report, pg 15):

- Cardiovascular adverse events such as arrhythmias, tachycardia, hypertension, orthostatic hypotension, myocardial infarction, congestive heart failure and stroke. QT prolongation and Torsade de pointes has been associated with amitriptyline use.
- Nervous system effects including frequent drowsiness, tremor, anxiety, insomnia, confusion and rarely extrapyramidal symptoms and dyskinesias.
- Constipation, nausea, vomiting, abdominal pain, and urinary retention can occur.

Teva stated that the greatest difference in frequency for the TCA treated group was for increased reporting of cardiovascular AEs, most notably heart failure. Nausea, dyspepsia and asthenia were also more prominent with TCA use over no use (and not seen on the SSRI or overall antidepressant most frequent AE tables), from which Teva concluded they are likely due to the TCA.

Of the six patients receiving TCAs that reported AE of anemia[74], Teva asserted that several had anemia due to another underlying condition or symptoms suggesting such. These included a subject with purpura and stools positive for occult blood with normal platelet count, with subject with esophagitis and renal cell cancer, a subject with recurrent prostate cancer and a subject with multiple chronic medical problems who died of ischemic bowel. Two patients (TVP-1012/123 #16016 and TVP-1012/135 #371) had mild/moderate AE of anemia that did not result in discontinuation of the study drug (Teva Antidepressant Report, pg.16).

9.3.5 Discontinuations Due to Adverse Events

Teva reported that there was no overall increase in early termination due to AE in patients treated with antidepressants and rasagiline (7.3%, 12.3 reports/100 PYs) compared to subjects receiving rasagiline alone (11.5%, 13.6 reports/100 PYs)[75]. The sponsor stated that twenty patients terminated the study early due to AE while receiving antidepressants: 12 were receiving SSRIs, 2 were receiving TCAs, 1 was receiving trazodone and 4 were receiving a combination of antidepressants. Teva believed that one patient (TVP-1012/123 #15813) should not be considered in this count as she started amitriptyline on the same day she terminated the study due to a gastrointestinal disorder. Teva stated that all of these discontinuing patients were receiving levodopa, except for one subject who discontinued due to pruritis (Teva Antidepressant Report, pg. 20).

[73] Teva referenced a study by Martindale et al.
[74] Sponsor Post-Text Table 21, Teva Antidepressant Report, pg. 52
[75] Sponsor Post-Text Table 25, Teva Antidepressant Report, pg. 74

The adverse events leading to discontinuation in these subjects[76] were: abdominal pain (3 subjects), asthenia (1 subject), back pain (1 subject), fall (1 subject), fever (1 subject), headache (1 subject), malaise (1 subject), hypertension (1 subject), syncope (1 subject), anorexia (1 subject), gastrointestinal disorder (1 subject), gastrointestinal hemorrhage (1 subject), anemia (1 subject), weight loss (2 subjects), arthralgia (1 subject), agitation (1 subject), anxiety (2 subjects), delusions (1 subject), depression (4 subjects), dyskinesia (2 subjects), hallucinations (2 subjects), hostility (1 subject), hyperkinesias (1 subject), manic reaction (1 subject), nystagmus (1 subject), sleep disorder (2 subjects), tremor (1 subject), pruritus (1 subject), melanoma (1 subject), eye disorder (1 subject), anuria (1 subject) and dysuria (1 subject).[77]

Teva also presented discontinuations due to AEs in subjects receiving antidepressants as descending order of difference in time-adjusted frequency, as per the table below.

FDA Table 42: Descending Order of Time-Adjusted Frequencies of AEs Leading to Discontinuation for Use and Non-Use of Antidepressants for All PD Subjects Exposed to Rasagiline (Cohort 9)(Adapted from Sponsor Table 10, Teva Antidepressant Report, pg. 21)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Concomitant use of Antidepressants		USE vs. NO USE
	YES (N=275, Patient-Years=349.2)	NO (N=1086, Patient-Years=1767.5)	
	No. of Reports Per 100 Patient Years	No. of Reports Per 100 Patient Years	
DEPRESSION	1.1	0.1	1.1
ABDOMINAL PAIN	0.9	0.2	0.7
ANURIA	0.6	.	0.6
ANXIETY	0.6	.	0.6
SLEEP DISORDER	0.6	0.1	0.5
WEIGHT LOSS	0.6	0.1	0.5
LIVER FUNCTION TESTS ABNORMAL	.	0.5	-0.5
DIZZINESS	.	0.5	-0.5
NAUSEA	.	0.5	-0.5

*AEs with an absolute difference of at least 0.5 report/100 patient-years in Use vs. No Use

Reviewer comment: *As with the overall and serious adverse events, based upon a small number of cases the above data does not demonstrate a pattern of discontinuations beyond what might be expected through either rasagiline or antidepressant administration singly.*

9.4 Sponsor Conclusions

[76] Sponsor Post-Text Table 25, Teva Antidepressant Report, pg. 74
[77] As the number of AEs leading to discontinuation exceeds the 20 antidepressant-treated subjects Teva stated discontinued prematurely, presumably more than one AE led to discontinuation for some subjects.

The sponsor summarized their findings and conclusions on concomitant rasagiline and antidepressant use as follows:

- No cases of serotonin syndrome were observed in the rasagiline development program as per the sponsor search criteria.
- Many of the neuropsychiatric, cardiovascular and gastrointestinal AEs that were noted with concomitant use of rasagiline and antidepressants have been previously reported with antidepressant treatment alone.
- There was no overall increase in early termination due to AE in patients treated with antidepressants and rasagiline.

Since the numbers and length of exposure may not be adequate to rule out the possibility of an untoward reaction from combining these agents, and since the mechanisms of these reactions are not fully understood, Teva stated that the concomitant use of rasagiline and antidepressants should be undertaken with caution. The sponsor acknowledged that a section in labeling describing concomitant antidepressant use during rasagiline clinical trials would be of value to the prescribing physician (Teva Antidepressant Report, pg. 23).

9.5 FDA Conclusions

The sponsor has provided data documenting the lack of apparent serotonin syndrome cases within the rasagiline development program, as well as data suggesting that serious adverse events are not strongly associated with concomitant antidepressant and rasagiline usage. However, the sponsor acknowledges that the overall exposure to these antidepressants was limited in the rasagiline development program with regards to the number exposed. This reviewer would also add that the exposure in the rasagiline development program was inadequate in regards to antidepressant dose, in light of what patients may receive concomitantly in regular clinical treatment with antidepressants.

Given this lack of adequate exposure, coupled with rare but potentially fatal case reports of serotonin syndrome in another MAO inhibitor used in the treatment of Parkinson's disease (selegiline), I recommend that the language within the FDA proposed labeling (see Attachment 12.1 of this review) be maintained, and that placement in the WARNINGS section is appropriate. Upon review of the above sponsor data I would now recommend the addition of:

- Further language clearly advising physicians that the antidepressant doses on which labeling data was based were lower than those frequently used in the treatment of depression should be inserted. The proposed labeling sent with the Approvable Letter notes the small number of subjects exposed, but does not stress the restricted doses.
- A stronger caution against co-administration of antidepressants that were excluded from the rasagiline development program due to prior serious reactions with other

MAOIs, such as fluoxetine and fluvoxamine, as well as those for which only single digit subject exposures occurred in the development program, such as venlafaxine.

If rasagiline receives FDA approval, this issue should receive close monitoring in the post-marketing period.

10. RESPONSE TO APPROVABLE LETTER: SPONSOR SAFETY UPDATE

10.1 Rasagiline Exposure

Teva stated that a total of 1991 subjects who participated in the rasagiline clinical development program were included in the safety database for the Response to Approvable Letter Safety Update. Of these, 1584 subjects (comprised of Parkinson's disease (PD) patients, Alzheimer's disease (AD) patients and healthy volunteers) were exposed to rasagiline for a total of 2375 person-years.[78] Exposure by individual studies in the rasagiline development program (and by combined treatment groups) are presented in the table below (Response to Approvable Letter Safety Update, pg. 29).

FDA Table 43: Number of Subjects and Exposure (Years) by Study and Study Drug (Adapted from Sponsor Table 1, Response to Approvable Letter Safety Update, pg. 29)

Pre-Approval Update of Rasagiline ISS:	Rasagiline		Placebo****		Entacapone		All
	No. of Subjects	Subject Years	No. of Subjects	Subject Years	No. of Subjects	Subject Years	No. of Subjects
Protocol Number							
TVP-1012/111	7	0.9	3	0.4	.	.	10
TVP-1012/112+TVP-1012/113	63	130.3	13	2.9	.	.	70
TVP-1012/121	4	0.6	1	0.2	.	.	5
LARGO+TVP-1012/123+TVP-1012/124	396	318.2	229	78.7	227	194.6	687
TVP-1012/132	14	2.5	6	1.2	.	.	20
PRESTO+TVP-1012/135+ TVP-1012/135OL (Open-Label)	436	549.6	159	73.8	.	.	472
TVP-1012/231	43	8.2	13	2.5	.	.	56
TEMPO**+TVP-1012/233	398	1352.2	138	63.4	.	.	404
Others***	223	12.7	44	3.4	.	.	267
All	1584	2375.3	606	226.4	227	194.6	1991

* Exposure calculations assume 100% compliance in the interval between the first and last doses of test medication

** Includes both study phases

*** Others include Phase I Studies (TVP-1012/421, TVP-1012/422, TVP-1012/423 TVP-1012/424, TVP-1012/425, TVP-1012/426, TVP-1012/427, TVP-1012/430, CC547, CD596, P94159 and AD patients (TVP-1012/311).

**** The majority of the placebo patients in studies TEMPO, LARGO, PRESTO and TVP-1012/112 continued in the extension studies and were treated with rasagiline

[78] In addition to the 1584 subjects exposed to rasagiline, Teva stated that the safety database included 186 placebo subjects (44 person-years) and 221 entacapone subjects (188 person-years).

For Cohort 9 (All PD patients Exposed to Rasagiline)[79], Teva stated that during the clinical development program, a total of 1361 patients were exposed to rasagiline for a total of 2363 patient-years. The sponsor stated that the majority (≥ 80%) of the patients were exposed to rasagiline 1 mg/day or to a higher dose. Overall, the sponsor stated that long-term exposure to rasagiline included 858 person-years on monotherapy, 400 person-years on levodopa adjunct therapy (non-fluctuating patients) and 593 person-years on chronic levodopa therapy (fluctuating patients) (Response to Approvable Letter Safety Update, pg. 6, pg. 29).

10.2 Update Period and Datalock Date

Teva stated that the database for the post-Approvable Letter safety update included data from all study visits in ongoing, open-label studies performed until February 15, 2004. This represents an additional exposure of approximately five months since the 120-day safety update, which included data accumulated until September 2003.[80]

For completed studies, the sponsor reported that the datalock date was January 11, 2004 for TVP-1012/123 (LARGO Adjunctive Open-Label Extension) and February 29, 2004 for TVP-1012/135 (PRESTO Adjunctive Open-Label Extension). The sponsor stated that reports from all deaths, SAEs and discontinuations due to AE received between October 1, 2003 and July 21, 2004 were provided in the safety update (Appendix 11.4)(Response to Approvable Letter Safety Update, pg. 24).

10.3 Sponsor Analysis Cohorts

Although described within my original NDA review, I have included the descriptions of the sponsor's analysis cohorts herein for ease of reference in the subsequent discussion of the safety update results below:

Placebo-Controlled Cohorts:

Cohort 1: Placebo-Controlled Studies without Levodopa Treatment. This cohort consisted of early PD patients treated with rasagiline 1 mg/day (N=149), rasagiline 2 mg/day (N=146), or placebo (N=151) without concomitant levodopa. Cohort members were subjects from the placebo-controlled phase of the monotherapy trial TEMPO and TVP-1012/231 (a ten-week, placebo-controlled study in 56 PD patients not previously treated with LD.)

Cohort 2: Placebo-Controlled Studies in Levodopa-Treated Fluctuating Patients. This cohort combined data collected from the rasagiline 1 mg/day (N=380) and placebo

[79] A full description of the data analysis cohorts created by the sponsor is provided in Section 4.1.3 of the Primary Safety Review of the original NDA, dated July 5, 2004.
[80] The exact date of the datalock for the 120-day safety update ranged from September 11, 2003 to September 29, 2003 for the various studies ongoing at that time.

(N=388) groups from the LARGO and PRESTO trials of rasagiline as adjunct to levodopa. Approximately 64% of subjects were receiving concomitant dopamine agonists (ISS Table 56.)

Rasagiline-Treatment Cohorts:

Cohort 3: Rasagiline Monotherapy – Any Treatment Duration. Teva described this cohort as including patients treated with rasagiline monotherapy from TEMPO (both phases) and its open-label extension (TVP-1012/233). Patients could not be taking dopamine agonists at the time of entry into TEMPO; however, approximately 46% of the cohort had dopamine agonists added to their PD regimen during the trial and its extension (ISS 8.1.2.1).

Cohort 4: Rasagiline Monotherapy – Long Term Treatment. This is a subset of 252 participants from Cohort 3 who were treated with rasagiline monotherapy for at least one year (median exposure of 2.9 years). The sponsor states that approximately 53% of these patients had dopamine agonists added to their PD regimen during the trial and its extension (ISS 8.1.2.2).

Cohort 5: Rasagiline Treatment: Rasagiline Treatment in LD-Treated Non-Fluctuating Patients – Any Treatment Duration. This cohort was composed of 154 participants from TEMPO (the active treatment phase), and/or its open label extension for which levodopa therapy was added to rasagiline monotherapy. The sponsor states that some of the patients in this cohort may have become fluctuators as their disease progressed.

Cohort 6: Rasagiline Treatment: LD-Treated Non-Fluctuating Patients – Long Term Treatment. Teva stated this cohort represents an 82 participant subset of Cohort 5 who received levodopa in addition to rasagiline for at least one year.

Cohort 7: Active Treatment: LD-Treated Fluctuating Patients – Any Treatment Duration. This cohort consists of fluctuating PD patients treated with rasagiline adjunct therapy in studies LARGO, the LARGO extension (TVP-1012/123), PRESTO, the PRESTO extension (TVP-1012/135), TVP-1012/112[81] and its extension (TVP-1012/113).

Cohort 8: Active Treatment: LD-Treated Fluctuating Patients – Long Term Treatment. Teva describes this cohort as a subset of 249 participants from Cohort 7 who were treated with rasagiline adjunct therapy for at least one year.

[81] TVP-1012/112 is a double-blind, randomized, placebo-controlled trail in LD-treated PD patients receiving 0.5 mg rasagiline, 1.0 mg rasagiline or placebo for 12 weeks.

Cohort 9: All PD Patients Ever Exposed to Rasagiline. This cohort was comprised of the 1537 Parkinson's disease patients ever exposed to rasagiline (120 Day Safety Update Table 2).

10.4 Deaths

Teva stated that two additional deaths were reported during the update period, as described below (Approvable Response Safety Update, pg. 56):

1. **TVP-1012/233 #287** (Cohort 5 and 6): This 79 year old woman with Parkinson's disease and a history of hypertension, cardiomyopathy and angina, esophageal reflux disease, hypothyroidism, arthritis, anxiety/depression, hypercholesterolemia and urinary incontinence was treated with rasagiline for 5.9 years. She presented with acute metabolic acidosis and renal failure secondary to an ischemic bowel, declined surgical intervention and subsequently died.
2. **TVP1012/Compassionate Use #41504:** This 71 year old man with a history of cerebrovascular accident and angina pectoris was treated with rasagiline for 1.8 years. He fractured a rib secondary to a fall and developed bronchopneumonia that did not respond to parenteral antibiotic treatment.

Reviewer comment: *I reviewed the full narratives[82] for these two deaths, and found the sponsor's descriptions above to be accurate and appropriately complete. When taken in combination with the listing of deaths in the safety review of the original NDA (Section 4.6.1, Table 19), these two additional deaths do not create a discernable pattern of deaths among rasagiline-treated patients. For reference, there were 21 deaths among rasagiline-treated subjects at the time of the original NDA review, attributed to the following causes: cerebrovascular disorder (n=6), sudden death (n=2), ruptured aneurysm (n=1), pneumonia (n=2), cancer (n=4, including n=1 due to melanoma), accidental causes (n=1), complex/multiple causes (n=2), and cause unknown (n=3).*

Teva summarized that during the entire rasagiline clinical program, a total of 34 patients died: 23 patients receiving rasagiline (22 PD patients and one Alzheimer's disease patient), 5 PD patients receiving placebo and 6 PD patients receiving entacapone and levodopa. When the placebo-controlled portions of the pivotal studies were combined, the risk of death was lower in the rasagiline treatment group (0.5%; 4/810), than in the placebo (1%; 5/526) and entacapone (1.3%; 3/277) group. The sponsor stated that the overall risk of death for *all PD patients* in the development program was 1.6% on rasagiline (22/1361), 0.9% on placebo (5/562), and 2.6% on entacapone (3/227). The rate of deaths over time for these three groups was 10 per 1000 person-years (PYs) for rasagiline (22/2326 PYs), 22 per 1000 PYs for placebo (5/223 PYs) and 16 per 1000 PYs for entacapone (3/194 PYs)(Response to Approvable Letter, pg. 56).

[82] The narratives for the two deaths were provided by the sponsor in Appendix 11.4 of the Response to Approvable Letter Safety Update.

Reviewer comment: *Interpretation of these pooled mortality risks and rates is complicated by the fact that such pooling combines rasagiline monotherapy and adjunctive therapy trials. Mortality rates in the untreated early and advanced PD populations differ substantially, so one would expect those differences to be reflected in the rates described above. Because an entacapone arm was only included in adjunctive studies, it is not unexpected that the mortality rate in that group is higher than the rasagiline rate which combines early and advanced PD patient trials. It would be more useful to look at the comparative mortality rates within Cohort 1 (monotherapy) and Cohort 2 (adjunctive therapy) cohorts.*

A request for this information was sent to the sponsor. For Cohort 1, Teva responded[83] that no deaths were reported during the monotherapy placebo-controlled studies. For Cohort 2, the sponsor provided the following table:

FDA Table 44. Combined PRESTO and LARGO (Cohort 2) Mortality Rates (Adapted from Sponsor Table 1, Teva E-Mail Communication received April 18, 2005)

PRESTO+LARGO	Rasagiline 0.5 mg	Rasagiline 1 mg	Placebo**	Entacapone
Number of Patients	164	380	388	227
Patient Years	76.1	146.7	147.3	74.4
Number of Deaths	1	3	4	3
Rate (Number of Deaths/Number of Patients)	0.61	0.79	1.03	1.32
Incidence Rate per 1000 PY* (Number of Deaths/Patients Years*1000)	13.14	20.44	27.15	40.34

*Patient years
**One patient (LARGO study, screening #141401) died before randomization and therefore was not included in the CRF tables and listings

Teva commented that higher death and incidence rates were observed in the entacapone and placebo groups as compared to the rasagiline treatment groups.

10.5 Serious Adverse Events

Teva noted that their SAE analysis encompassed reports within the sponsor's safety database at the time of the cut-off for the safety update report. The sponsor also provided summaries and narratives of newly reported SAEs received after the cut-off date until July 21, 2004. The sponsor further stated that, in addition to the new cases reported during the update period, another 28 previously reported SAEs (occurring among 12 patients) were added to the SAE listings and tables of this report. Teva explained that these 28 cases had been incorrectly recorded as non-serious AEs in the original ISS due to a data programming error. Teva noted that all of these AEs had already been submitted as SAE narratives in previous safety reports. A table listing these 28 adverse events is provided below (Response to Approvable Letter Safety Update, pg. 57).

[83] Sponsor response sent via electronic mail, received April 18, 2005.

FDA Table 45: SAEs Incorrectly Reported as Non-Serious in the Original ISS and the 120-Day Safety Update (Adapted from Sponsor Post-Text Table 40, Response to Approvable Letter Safety Update, pg. 130)

Patient No.	COSTART Term	No. of Reports/Comment
TVP-1012/123 #16210	Gastrointestinal hemorrhage	2 reports on the same day
TVP-1012/133 #77	Accidental injury	3 reports on the same day
TVP-1012/135OL #134	Vascular disorder	2 reports on the same day
TVP-1012/133 #265	Accidental injury	2 reports on the same day
TVP-1012/135 #272	Esophagitis	1 report
TVP-1012/133 #555	Confusion	2 reports on the same day
TVP-1012/233 #9	Skin melanoma	2 reports on the same day
TVP-1012/233 #105	Accidental injury	2 reports on the same day
TVP-1012/233 #261	Sepsis and urinary tract infection	2 reports each, on the same day
TVP-1012/233 #268	Gastrointestinal disorder	2 reports on the same day
TVP-1012/233 #287	Syncope	4 reports on the same day
TVP-1012/233 #407	Accidental injury	4 reports on the same day

Teva provided the following information updating SAEs in the long-term and overall rasagiline treatment cohorts:

Reviewer comment: *The cohorts presented in the Response to Approvable Letter Safety Update did not have a placebo control, which clearly limits the interpretation of the percentages and time-adjusted frequencies of adverse events.*

Cohort 4: Rasagiline Treatment without Levodopa: Long-Term Treatment

Teva stated that SAEs were reported by 26.6% of patients in this cohort, with a time-adjusted frequency of 17.2 reports /100 PYs. This compares to 21.4% of Cohort 4 patients reporting SAEs (and a time-adjusted frequency of 14.2 reports/100 PYs) in the original ISS. The sponsor noted that 4.4% (148/3333) of all AEs reported for the cohort were serious (Response to the Approvable Letter Safety Update, pg. 57).

Teva stated that similar to that reported in the original ISS, the body system with the highest time-adjusted frequency of SAEs was the cardiovascular (5.5 versus 5.1 reports/100 patient-years in the original ISS), followed by the body as a whole (3.6 versus 2.5 reports/100 patient-years in the original ISS). The sponsor stated that compared to the original ISS, the largest increase in SAEs occurred for the nervous system, with the addition of six patients reporting nervous system SAEs (Response to the Approvable Letter Safety Update, pg. 57).

Reviewer comment: *I reviewed the sponsor tables summarizing SAEs in the Response to Approvable Letter Safety Update (Post-Text Tables 41) and the original ISS (Post-Text Table 53), and the additional six patients contributing to the nervous system SAEs*

reported the following adverse events: confusion (n=2), convulsion (n=2), dizziness (n=1), extrapyramidal syndrome (n=1), hallucinations (n=1), spinal stenosis (n=2) and abnormal thinking (n=1).

Teva described the following two newly reported SAEs, which were not included in the safety database due to receipt after the datalock date:

- **TVP-1012/233 #543** presented with a sigmoid volvulus but continued the study drug despite the SAE.
- **TVP-1012/233 #176** had back pain due to a vascular structure at T9-10.

Cohort 5: Rasagiline Treatment of Levodopa-Treated Non-Fluctuating Patients: Any Treatment Duration

The sponsor stated that SAEs were reported in 27.3% of patients in this cohort with a time-adjusted frequency of 31.4 report/100 PYs. Teva noted that of all AEs reported, 6.9% (136/1976) were serious. Teva reported that the overall incidence and time-adjusted frequency of SAEs in the 120-day update were similar (26.2% and 27.1 reports/100 patient-years, respectively.) Teva stated that although there was an increase in time-adjusted frequency of SAEs of the cardiovascular system as compared to the 120-day safety update (7.6 versus 5.7 reports/100 patient-years), their risk remained stable [8.6% (17 patients) versus 8.2% (15 patients)] (Response to Approvable Letter Safety Update, pg. 58).

Reviewer comment: *Cardiovascular adverse events are discussed in more detail in Section 10.5.1 below.*

The sponsor stated that the majority of SAEs added during the update period had previously been reported as narratives in the 120-day safety update. Teva noted that there were no new SAEs of myocardial infarction, cerebrovascular accident or nervous system SAEs during this update period. The sponsor summarized the following newly reported SAEs that were not included in the safety database due to receipt after the datalock date:

- **TVP-1012/233 #157** underwent a right total knee arthroplasty
- **TVP-1012/233 #158** was diagnosed with bladder cancer
- **TVP-1012/233 #166** was admitted for IV immunoglobin therapy for an ongoing polyneuropathy. Two months later the patient fell and was hospitalized.
- **TVP-1012/233 #174** underwent elective mediastinoscopy with diagnosis of noncaseating sarcoidal granuloma.
- **TVP-1012/233 #40** was admitted for a total hip replacement due to avascular necrosis of the hip.
- **TVP-1012/233 #10** was hospitalized for elective lumbar laminectomy.
- **TVP-1012/233 #103** fractured his elbow after a fall, requiring surgical repair.
- **TVP-1012/233 #322** was hospitalized for a radical prostatectomy due to prostate cancer.

- **TVP-1012/233 #102** was hospitalized for treatment of severe gastritis and dehydration.

Cohort 6: Rasagiline Treatment in Levodopa-Treated Non-Fluctuating Patients: Long-Term Treatment

Teva stated that SAEs were reported in 33.9% of patients in this cohort. Of all the AEs reported, 6.8% (118/1726) were serious. The sponsor asserted that time-adjusted frequency of SAEs by body system remained stable or decreased when compared to Cohort 5, and no specific SAE showed a prominent increase in frequency for this cohort (Response to Approvable Letter Safety Update, pg. 59).

Cohort 9: All PD Patients Ever Exposed to Rasagiline

Teva stated that SAEs occurred in 22.8% of patients treated with rasagiline, and that for all AEs reported, 6.3% (687/10,946) were SAEs. The sponsor reported that time-adjusted frequency of SAEs for this cohort was 29.1 reports/100 PYs, comparable to that of the original ISS (24.5 reports/100 PYs). Teva noted an increase of 1.1 to 1.8 reports per 100 PYs between the current update and both previous safety reports[84]. The sponsor asserted that this was attributable to increased reporting of arthritis and joint disorder when patients had elective joint replacement or lumbar disc surgery (Response to Approvable Letter Safety Update, pg. 59).

Teva noted that when SAEs for Cohort 9 in the Post-Approvable Letter safety update are compared to both previous sponsor safety updates, small differences in time-adjusted frequency are noted for most SAEs, as presented in the two following tables:

FDA Table 46: Difference between the Post-Approvable Safety Update Versus the Original ISS (Adapted from Sponsor Table 32, Response to Approvable Letter Safety Response, pg. 60)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)		Original ISS Rasagiline (N=1187, Patient-Years=1462.9)		Difference (%)
	No. of Patients	% of Patients	No. of Patients	% of Patients	
ACCIDENTAL INJURY	37	2.7	14	1.2	1.5
SYNCOPE	16	1.2	7	0.6	0.6
ARTHRITIS	11	0.8	3	0.3	0.6
JOINT DISORDER	16	1.2	7	0.6	0.6
PSYCHOSIS	9	0.7	1	0.1	0.6
PNEUMONIA	12	0.9	3	0.3	0.6
INFECTION	11	0.8	4	0.3	0.5
CORONARY ARTERY DISORDER	12	0.9	4	0.3	0.5
EXTRAPYRAMIDAL SYNDROME	10	0.7	3	0.3	0.5
SURGERY & PROCEDURES	13	1.0	6	0.5	0.4

*Ten most common SAEs in the pre-approval update sorted by the difference in incidence of pre-approval vs. original ISS

[84] The two previous safety reports included the original ISS and the 120-day safety update.

FDA Table 47: Time-Adjusted Frequency of SAEs for Cohort 9 in Descending Order of Difference between the Post-Approvable Safety Update Versus the 120-Day Safety Update (Adapted from Sponsor Table 31, Response to Approvable Letter Safety Response, pg. 59)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	No. of Reports Per 100 Patient-Years		
	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)	120-Day Safety Update Rasagiline (N=1360, Patient-Years=2017.2)	Difference
ACCIDENTAL INJURY	2.2	1.4	0.8
JOINT DISORDER	1.0	0.5	0.5
SURGERY & PROCEDURES	0.7	0.4	0.3
CORONARY ARTERY DISORDER	0.6	0.3	0.2
GASTROINTESTINAL HEMORRHAGE	0.4	0.2	0.2
ARTHRITIS	0.5	0.3	0.2
PSYCHOSIS	0.4	0.2	0.2
PNEUMONIA	0.6	0.4	0.2
INFECTION	0.6	0.4	0.2
ATRIAL FIBRILLATION	0.6	0.5	0.1

*Ten most frequent SAEs in the pre-approval update sorted by the difference in time-adjusted frequency of pre-approval vs. 120-day update

Reviewer comment: *It is somewhat unexpected to see the percentage of patients reporting SAEs going up in these cohorts, as one would expect that those patients sensitive to rasagiline would have dropped out of the trials earlier, leaving patients relatively less subject to potential rasagiline related AEs. The increases in percentage of patients reporting SAEs may be related to advancing underlying disease, as would be suggested by the types of SAEs reported (e.g., accidental injury, pneumonia, infection, syncope).*

10.5.1 Cardiovascular Adverse Events: Myocardial Infarction

Within the sponsor's response to the FDA Approvable Letter request for tyramine data, the sponsor reported that the relative risk of myocardial infarction (MI) was five-fold higher in rasagiline group (4/805; 0.5%) than in the placebo group (1/757; 0.1%) for the pooled placebo-controlled portions of the three pivotal trials. These and other cardiovascular adverse events were presented by the sponsor in the following table (Response to Approvable Letter: Tyramine, pg. 12).

FDA Table 48: Incidence of Death and Cardiovascular Serious Adverse Events in TEMPO, PRESTO and LARGO (Total N = 1,563)(Adapted from Sponsor Table 4, Response to Approvable Letter: Tyramine, pg. 12)

	Rasagiline** N=806 (% of patients)	Placebo/ Entacapone *** N=757 (% of patients)
Death (non-CV)	0	2 (0.4%)
Death (CV)	4 (0. 5%)	6 (0.8%)
CVA	3 (0.4%)	3 (0.4%)
MI	4 (0.5%)	1 (0.1%)
Hypertensive and Vascular Emergencies	0	2 (0.3%)

* There were no serious CV events in TEMPO patients on 2 mg daily
** 0.5mg. 1mg. 2mg rasagiline
*** Including Placebo Run-in period

CV events -PHV data base, March 2003.
Death

Reviewer comment: *Although the absolute number and difference between the number of cases in the rasagiline and placebo treatment groups is small (4 rasagiline versus 1 placebo), the relative difference between the two (0.5% rasagiline versus 0.1% placebo) warrants further examination. Because risk of MI may differ by age, the risk of MI must be examined separately in the monotherapy (early PD, mean age 61.3 years) and adjunctive therapy (late PD, mean age 64.2 years) cohorts.*

10.5.1.1 MI Rates Per Person-Year Exposure

The sponsor did not provide an analysis on myocardial infarction based upon person-years exposure during the pooled placebo-controlled phases of the three pivotal trials. However, during these placebo-controlled phases, a total of 344 person-years (PYs) was accumulated by subjects treated with rasagiline (121 PYs TEMPO, 77 PYs LARGO, 146 PYs PRESTO), and 211 PYs by subjects treated with placebo (63 PYs TEMPO, 74 PYs LARGO, 74 PYs PRESTO). Using these numbers for the denominator, the rate of myocardial infraction per person-years in the Cohort 1 (monotherapy) was 1.6 per 100 PYs (2/121) for the rasagiline treatment group. In Cohort 2 (adjunctive therapy: LARGO and PRESTO), the rate was 0.9 per 100 PYs (2/223) in the rasagiline treatment group. No placebo subject in any of the three pivotal trials experienced an MI, although one subject did so prior to randomization.

Reviewer comment: *The sponsor included a subject who experienced an MI prior to randomization as the single MI in a "placebo" subject. I believe this is not appropriate (the subject was not treated with placebo), and by excluding this subject the number of placebo patients with MI is reduced from one to zero.*

It is notable that the rasagiline-treated adjunctive therapy subjects had approximately half the rate of MIs during the placebo-controlled phase as the monotherapy subjects, despite a somewhat older mean age. However, the number of events per group is small, making such comparisons unstable.

10.5.1.2 MI Case Characteristics

Teva stated that the five patients who experienced myocardial infarction during the placebo-controlled phase of the pivotal trials were distributed among the studies as follows: three occurred in the adjunct therapy study LARGO (two receiving rasagiline, one during run-in period prior to rasagiline treatment) and two in the monotherapy study TEMPO (both receiving rasagiline)(Response to Approvable Letter: Tyramine, pg. 70). The sponsor stated that no reports of MI occurred in treatment group during the adjunctive therapy study PRESTO (PRESTO Study Report, pg. 150).

Summaries of each of the five cases are provided below, and more detailed narratives are included in Attachment 12.8 of this review.

Placebo-Controlled Pivotal Trials: Rasagiline-Treated Subjects

1. **TEMPO (Monotherapy) #179:** This 72 year old man discontinued rasagiline (1 mg/day) on January 15, 1999 (49 days after study entry) due to complications of an elective surgery to repair an abdominal aortic aneurysm. He experienced an intraoperative myocardial infarct and postoperatively had residual foot drop and toe tip necrosis as a result of lower extremity ischemia. The sponsor reported that the patient discontinued participation in the study because he was not ambulatory (TEMPO Study Report, pg. 125).

2. **TEMPO (Monotherapy) #249:** This 47 year old man with a history of hypercholesterolemia was hospitalized with a myocardial infarction on day 323 of treatment with rasagiline (2 mg/day). TPA reperfusion was followed by a four-vessel coronary artery bypass graft. The patient remained on study medication throughout the event.

3. **LARGO (Adjunctive Therapy) # 90112:** This 87 year old man (rasagiline 1 mg/day) experienced a subclinical myocardial infarction sometime during the study, which was detected by the presence of septal Q waves during an ECG performed on the subject's termination visit. Teva reported that the patient completed the study as per the protocol (LARGO Study Report, pg. 141).

4. **LARGO (Adjunctive Therapy) # 50506:** This 68 year old man (rasagiline 1 mg/day) underwent two ECGs prior to receiving the study drug: the first read as demonstrating septal infarction and the second not. Teva stated that the subject's termination ECG was considered to have evidence of a "new" infarction in comparison to the second pre-drug tracing (LARGO Study Report, pg. 162).

Placebo-Controlled Pivotal Trials: Placebo-Treated Subjects

5. **LARGO (Adjunctive Therapy) # 141401**: This 72 year old woman died after experiencing an acute myocardial infarction prior to randomization (LARGO Study Report, pg. 143).

Reviewer comment: *Due to the small number of subjects and the indeterminate timing of two of the myocardial infarctions, it is difficult to assess any pattern of MI with regards to duration of exposure to rasagiline.*

10.5.1.3 Myocardial Infarction in the Original NDA Safety Database

In the safety database provided with the original NDA submission, one subject in the rasagiline placebo-controlled monotherapy cohort (Cohort 1) had experienced a myocardial infarction, compared to none in the placebo group. In Cohort 2 (placebo-controlled adjunctive therapy), myocardial infarction occurred in one subject receiving rasagiline and in none receiving placebo. In Cohort 9 (all PD patients exposed to rasagiline), myocardial infarction occurred in 6 patients (0.4%)(Rasagiline NDA Safety Review, pg. 136).

Of the 21 deaths occurring in rasagiline-treated subjects at the time of the original NDA submission, none were attributed to myocardial infarction, although six were classified as cerebrovascular accidents, two were categorized as sudden death and three were due to unknown causes (Rasagiline NDA Safety Review, pg. 41).

10.5.1.4 Reviewer Conclusions on MI in the Rasagiline Development Program

Although there is an elevation in the absolute number of MIs experienced by rasagiline-treated subjects (n=4) versus placebo-treated subjects (n=1) in the placebo-controlled portions of the pooled pivotal studies, several factors mitigate this relative risk. First, the 4:1[85] rasagiline treatment to placebo elevation is only seen when monotherapy and adjunctive therapy pivotal studies are combined, and the appropriateness of this pooling is questionable given the differences in subject age and disease severity. No consistent pattern of MI elevation in the rasagiline-treatment groups was apparent when the three studies were examined individually, although the small absolute number of cases in the pooled studies makes subgroup analysis even more unstable. Secondly, for two of the four cases in the rasagiline-treated subjects either the occurrence or the attribution of the MI to rasagiline is uncertain. Specifically, one MI (TEMPO #179) occurred as an intraoperative complication during an aortic aneurysm repair; in the other case (LARGO #50506), due to discrepant readings of the screening ECG, it was unclear if the myocardial infarction actually occurred during the study period. Finally, myocardial infarction was not among the causes of death for rasagiline-treated subjects throughout

[85] As mentioned previously in a reviewer comment, the single MI case the sponsor counted in the placebo group actually occurred prior to randomization. It is therefore more appropriate to consider the number of placebo cases as zero rather than one.

the development program, despite an age-group in which myocardial infarctions are not infrequent.[86]

10.6 Discontinuations Due to Adverse Events

Teva stated up until the time of the datalock for the safety update, premature discontinuation "due to adverse event" was reported for a total of 11.3% (n=150) of all PD patients ever exposed to rasagiline. When compared to the 120-day safety update by descending order of difference, the sponsor reported that no difference in incidence and time-adjusted frequency were noted for the AEs resulting in early termination. Teva supported this assertion with the two tables below (Response to Approvable Letter Safety Update, pg. 63).

***Reviewer comment**: The AEs leading to discontinuation that increased in risk and rate between the 120 day safety update and this current safety update are typical of events occurring in PD patients with advancing disease.*

FDA Table 49: Incidence of Adverse Events Resulting in Early Termination by COSTART Term and Descending Order of Difference* of Post-Approvable Letter Safety Update Versus the 120-Day Safety Update (Adapted from Sponsor Table 36, Response to Approvable Letter Safety Response, pg. 63)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)		120-Day Safety Update Rasagiline (N=1360, Patient-Years=2017.2)		Difference (%)
	No. of Patients	% of Patients	No. of Patients	% of Patients	
HALLUCINATIONS	18	1.3	14	1.0	0.3
EXTRAPYRAMIDAL SYNDROME	7	0.5	4	0.3	0.2
PSYCHOSIS	7	0.5	4	0.3	0.2
ACCIDENTAL INJURY	8	0.6	7	0.5	0.1
ASTHENIA	6	0.4	4	0.3	0.1

*At least two patients higher in the pre-approval database

FDA Table 50: Time-Adjusted Frequency of Adverse Events Resulting in Early Termination by COSTART Term and Descending Order of Difference* of Post-Approvable Letter Safety Update Versus the 120 Day Safety Update (Adapted from Sponsor Table 35, Response to Approvable Letter Safety Response, pg. 63)

[86] Within the rasagiline development program, there were three subjects whose death was classified as " cause unknown" and two whose death was classified as "sudden death." Although the details of these deaths are either unknown or uncertain, some or all of these five deaths could have been secondary to MI. However, as per their classification, the diagnosis of MI was not established in any of these deaths.

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	No. of Reports Per 100 Patient-Years		
	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)	120-Day Safety Update Rasagiline (N=1360, Patient-Years=2017.2)	Difference
HALLUCINATIONS	0.9	0.8	0.1
EXTRAPYRAMIDAL SYNDROME	0.3	0.2	0.1
PSYCHOSIS	0.3	0.2	0.1
ASTHENIA	0.3	0.2	0.1
DELUSIONS	0.1	0	0.1

*AEs with a higher time-adjusted frequency in the pre-approval database

Teva noted that five patients discontinued "due to AE" but did not have a specific AE associated with the drug discontinuation. Teva stated that these patients were not included in the tables summarizing the discontinuation due AE data (Response to Approvable Letter Safety Update, pg. 62). However, at the request of the DNDP, Teva subsequently assigned AEs to these subjects'[87] discontinuations, as described in Section 7 (Missing AE Attribution of Discontinuations) of this review.

10.7 Common Adverse Events

Teva presented updated safety data for the most frequent adverse events by cohort, as summarized below:

Cohort 4: Rasagiline Treatment without Levodopa: Long-Term Treatment

Teva stated that when ranked in descending order by time-adjusted frequency, the most commonly reported AEs in this cohort were infection (20 per 100 PYs; 37.7%), headache (15.9 per 100 PYs; 20.6%), accidental injury (14.5 per 100 PYs; 26.2%), pain (10.6 per 100 PYs; 15.5%), dizziness (10.3 per 100 PYs; 21.4%), arthralgia (10.1 per 100 PYs; 21%), back pain (9.1 per 100 PYs; 20.2%), nausea (8.6 per 100 PYs; 19.4%), peripheral edema (8.4 per 100 PYs; 17.9%) and sleep disorder (6.4 per 100 PYs; 18.7), similar to those reported in the original ISS (Response to Approvable Letter Safety Update, pg. 46).

***Reviewer comment**: I compared the frequency and incidence of the adverse events above with those reported in the original ISS (Post-Text Table 51), and agree with the sponsor assessment that these were not substantially different from those within the original ISS.*

Cohort 5: Rasagiline Treatment of Levodopa-Treated Non-Fluctuating Patients: Any Treatment Duration

Teva stated that when ranked in order of time-adjusted frequency, the most frequently reported AEs for this cohort were accidental injury (26.1 per 100 PYs; 28.3%), skin

[87] The five patients were identified by the sponsor as TVP-1012/133 #756, TVP-1012/133 #169, TVP-1012/133 #544, TVP-1012/233 #118 and TVP-1012/232 #179. The identification was received on April 18, 2005 in an electronic mail response to a prior FDA question.

carcinoma (16.4 per 100 PYs; 10.1%), infection (13.2 per 100 PYs; 21.2%), arthralgia (12.5 per 100 PYs; 18.2%), nausea (11.6 per 100 PYs; 21.7%), pain (11.3 per 100 PYs; 19.2%), skin benign neoplasm (11.3 per 100 PYs; 11.6%), dizziness (10.6 per 100 PYs; 14.6%), postural hypotension (9.9 per 100 PYs; 14.1%) and somnolence (9.2 per 100 PYs; 16.2%). Teva noted that the AEs demonstrating an apparent increase in time-adjusted frequency since the 120-day update were the two dermatologic AEs of skin carcinoma (12.8 per 100 PYs; 7.7%) and benign skin neoplasm (6.0 per 100 PYs; 7.1%)(Response to Approvable Letter Safety Update, pg. 47).

Reviewer comment: *In addition to the increase in skin carcinoma (16.4 per 100 PYs versus 12.8 per 100 PYs in the 120-day update) and benign skin neoplasm (11.3 per 100 PYs versus 6.0 in the 120-day day update), the time-adjusted frequency of melanoma was also elevated in comparison to the 120-day safety update (1.4 per 100 PYs in the current safety update versus 1.2 per 100 PYs in the 120-day safety update).*

Cohort 6: Rasagiline Treatment in Levodopa-Treated Non-Fluctuating Patients: Long-Term Treatment

Teva stated that compared to Cohort 5 (any treatment duration), this long-term cohort had similar time-adjusted frequency for most of the common AEs, which Teva commented suggested no cumulative effect for rasagiline therapy (Response to Approvable Letter Safety Update, pg. 47).

Reviewer comment: *I compared the time-adjusted frequencies of the most frequent adverse events in Cohort 5 (Sponsor Table 23) and Cohort 6 (Sponsor Table 24), and concur that there were no significant increases. Teva did not comment on changes in adverse events in comparison to the prior safety update. When compared to the most frequent adverse events in Cohort 6 within the 120-day safety update (Post-Text Table 44), the only AE showing a significant increase in the time-adjusted frequency was skin benign neoplasm (6.0 per 100 PYs in the 120-day safety update and 11.3 in the Post-Approvable Letter safety update). These increases in skin lesion frequency seen in this cohort and above may be related to the scheduled dermatological screening that was instituted during the development program when the melanoma signal was first identified.*

Cohort 9: All PD Patients Ever Exposed to Rasagiline

Teva stated that when ranked in descending order by time-adjusted frequency, the most frequent AEs included accidental injury (22.8 per 100 PYs; 20.5%), infection (17.6 per 100 PTs; 18.9%), headache (13.7 per 100 PYs; 11.2%), dizziness (13.3 per 100 PYs; 14.7%), arthralgia (11.5 per 100 PYs; 12.6%), nausea (11.1 per 100 PYs; 13.4%), pain (10.4 per 100 PYs; 11.8%) and back pain (9.7 per 100 PYs; 11.8%). Teva noted that accidental injury, infection, headache, dizziness and pain were among the most frequently reported AEs in the placebo groups, as well as the rasagiline-treated groups, of the original ISS. Teva further commented that dyskinesia and sleep disorder are expected

with dopaminergic therapy, and that the time-adjusted frequency of these events in the Post-Approvable safety update was similar to that in the original ISS and 120-day update (10.1, 10.1 and 9.4 per 100 PYs for dyskinesia and 9.7, 9.4 and 9.8 per 100 PYs for sleep disorder, respectively)(Response to Approvable Letter Safety Update, pg. 48).

Teva noted that the largest difference between the original ISS and the Response to Approvable Letter safety update were observed for the dermatologic AEs (skin carcinoma, benign skin neoplasm and skin disorder). The sponsor suggested that this is likely due to screening bias resulting from performance of regular full-body skin examinations. Teva provided the two tables below demonstrating the changes in time-adjusted frequencies of the most common adverse events from the original ISS, 120-day safety update and the Response to Approvable Safety Update (Response to Approvable Letter Safety Update, pg. 48).

FDA Table 51: Time-Adjusted Frequency of Adverse Events in Descending Order of Difference* for Cohort 9 in the Post-Approvable Letter Safety Update Versus the Original ISS (Adapted from Sponsor Table 26, Response to Approvable Letter Safety Update, pg. 49)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Rasagiline: No. of Reports Per 100 Patient-Years		
	Pre-Approval Update (N=1361, Patient-Years=2362.5)	Original ISS (N=1187, Patient-Years=1462.9)	Difference
SKIN BENIGN NEOPLASM	5.5	2.3	3.2
SKIN CARCINOMA	7.4	4.9	2.5
SKIN DISORDER	5.8	4.0	1.8
ACCIDENTAL INJURY	22.8	21.5	1.3
JOINT DISORDER	4.1	3.2	0.9
HALLUCINATIONS	5.6	4.9	0.8
PNEUMONIA	1.4	0.6	0.7
DYSKINESIA	10.1	9.4	0.6
PSYCHOSIS	0.6	0.1	0.6
AGITATION	0.6	0.1	0.5

* Ten most frequent AEs in the pre-approval update by the difference in time-adjusted frequency of pre-approval vs. original ISS

FDA Table 52: Time-Adjusted Frequency of Adverse Events in Descending Order of Difference* for Cohort 9 in the Post-Approvable Letter Safety Update Versus the 120-Day Safety Update (Adapted from Sponsor Table 27, Response to Approvable Letter Safety Update, pg. 49)

Pre-Approval Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Rasagiline: No. of Reports Per 100 Patient-Years		
	Pre-Approval Update (N=1361, Patient-Years=2362.5)	120-Day Safety Update (N=1360, Patient-Years=2017.2)	Difference
SKIN BENIGN NEOPLASM	5.5	3.8	1.8
ACCIDENTAL INJURY	22.8	21.1	1.7
SKIN CARCINOMA	7.4	6.3	1.2
JOINT DISORDER	4.1	3.1	1.0
SKIN DISORDER	5.8	4.8	0.9
URINARY TRACT INFECTION	6.9	6.1	0.8
HALLUCINATIONS	5.6	5.0	0.7
PERIPHERAL EDEMA	8.4	7.7	0.6
ELECTROCARDIOGRAM ABNORMAL	1.9	1.3	0.5
ARTHRITIS	3.5	3.0	0.5
HYPERTENSION	4.2	3.8	0.4

* Ten most frequent AEs in the pre-approval database by the difference in time-adjusted frequency of pre-approval vs. 120-day update

11. CONCLUSIONS AND RECOMENDATIONS

As per the FDA requests within the Approvable Action Letter issued in July 2004, Teva submitted additional data pertaining to unresolved safety concerns from the initial NDA review. These will be discussed in turn below:

11.1 Melanoma

11.1.1 Dose-Response Analysis

As per the request in the FDA Approvable Action letter, the sponsor performed a dose-response analysis for the 17 cases of treatment emergent melanomas (among 16 subjects) that had been identified at the time of the analysis.[88] For the denominator, person-year exposure per dose group was utilized, with subjects contributing time to each dose group they were exposed to.[89] For the numerator, the modal dose (the dose to which the subject was exposed for the longest period of time) was used to designate the dose level to which the melanoma cases were assigned. In their methodology, the sponsor also created a "0 mg" rasagiline group, which included placebo subjects (n=1) as well as subjects diagnosed with melanoma prior to treatment initiation (n=3). As the purpose of the dose-response analysis was to examine treatment emergent cases, the calculations were repeated by this reviewer, excluding the three cases diagnosed before treatment ensued. This resulted in a potential dose-response relationship for in situ and total melanomas:

- In Situ Melanomas:
  - 0 mg: 1 case 238 cases/100,000 PYs
  - 0.5 mg: 0 cases 0 cases per 100,000 PYs
  - 1.0 mg: 6 cases 393 cases per 100,000 PYs

[88] The most recent count of melanomas within the rasagiline development program during the writing of this report was 24, 20 of which were treatment emergent (See Attachment 12.2 of this review).
[89] For example, if a patient was treated with 0.5 mg initially and then later increased to 1 mg, the time they were treated with each dose was allotted to that dose.

- 2.0 mg: 4 cases 554 cases per 100,000 PYs

- Total (In Situ plus Invasive) Melanomas:
  - 0 mg: 1 case 238 cases/100,000 PYs
  - 0.5 mg: 2 cases 677 cases/100,000 PYs
  - 1.0 mg: 11 cases 720 cases per 100,000 PYs
  - 2.0 mg: 4 cases 738 cases per 100,000 PYs

I repeated the dose-response analysis after attributing cases to the dose the patient was on at time of diagnosis, instead of the modal dose. As only a few cases changed dose groups by using this approach, the results were similar to that above, although the dose-response relationship was somewhat diminished in the higher doses (1 and 2 mg). I would consider use of the modal dose as the most appropriate approach to the dose-response analysis, however, as in 15 of the 17 treatment-emergent cases[90] the modal dose represents the only or the large majority of the subject's dose exposure.

11.1.2 Comparison of EP002 Study Results with the AAD Screening Data

The sponsor conducted Study EP002 in 2,106 North American Parkinson's disease patients (at various stages of the disease), who had not been exposed to rasagiline. Subjects were recruited by a neurologist, who recorded the subject's Parkinson's disease history. The remainder of study participation consisted of a visit to a dermatologist, who conducted a single screening for skin cancers (with biopsy of any suspicious lesions), and who recorded the subject's history of skin cancers in the two-years prior to the study. The dermatologist also collected information on skin cancer risk factors.

Limitations of sponsor study EP002 included volunteer bias, which may have enriched the cohort with melanoma-prone subjects. In addition, the lack of medical records verification of self-reported retrospective melanomas in 72% of cases (53/74) could have introduced error due to patient confusion with other, more common forms of skin cancer. However, for the comparison with the AAD data, I included only melanomas diagnosed during the dermatologic screening of EP002.

The results of the dermatologic screening component[91] of study EP002 were compared with data from the American Academy of Dermatology (AAD) screening program. Both are North American populations screened for melanoma at essentially the same frequency (one time). The two populations differed in the following respects:

[90] The two subjects for whom the modal dose did *not* represent the only or the large majority of the patient's exposure were TVP-1012/233 #9 (1 mg: 1.31 years, 2 mg: 1.29 years) and TVP-1012/233 #64 (1 mg: 1.58 years, 2 mg. 1.3 years)(FDA Table 1, pg. 12).

[91] In addition to conducting a single dermatologic screening examination, Study EP002 collected data on skin cancers from the subjects' medical histories in the two-year period prior to study enrollment (the "retrospective cohort" component of the study.) These prior melanomas were excluded from the comparison with the AAD data, as I considered it more methodologically appropriate to compare the "one-time" screening in EP002 with the essentially "one-time" screening in the AAD.

- The primary difference was the presence of Parkinson's disease and its treatments in the EP002 cohort.
- The dates of screening differed between the two groups (1992-1994 for the AAD data, and 2003 for the EP002 data). Rates of melanoma are rising rapidly worldwide, and during the time period from 1993 to 2001 (the most recent SEER data), the age-adjusted rate of invasive melanoma for all races within the United States increased from 14.5 per 100,000 to 18.7 per 100,000, an approximately 28% increase. There could therefore be an increase in the number of melanomas in the EP002 study compared to the AAD data based solely on the screening epoch.
- The AAD was drawn exclusively from subjects within the United States, while in EP002 approximately 20% of subjects were from Canadian sites.
- Approximately 20% of AAD subjects underwent more than one annual screening.

For the comparison, melanoma rates (by age and gender) from the AAD screening program were applied to the population of the sponsor EP002 cohort study. The resulting number of melanomas expected as per the AAD rates were compared with the observed number of melanomas within the EP002 cohort study during the dermatologic screening exam. The comparison yielded the following result:

FDA Table 53: Observed to Expected Comparison in Sponsor North American Cohort Study EP002, using the AAD Screening Program as a Reference Population

Melanomas	**Number Observed** *	**Number Expected** **	**Obs./ Exp. Ratio**	**95% CI** ***
Invasive	4	3.3	1.2	0.33,3.1
In Situ	20	1.2	16.7	10.2, 25.7
Total	24	4.5	5.3	3.1, 7.9

* Number of melanomas diagnosed in North American through dermatologic screening
** Number of melanomas expected within rasagiline subjects as per the rates of the screened population within the AAD screening program

For total melanomas, there is a 5.3-fold increase in the number of melanomas within EP002 as compared to those expected number of melanomas as per the AAD age and gender specific rates. The most striking finding, however, is that the elevation in total melanomas is driven by an almost 17-fold increase in situ lesions, and a relatively small increase in invasive lesions. Although the significant elevation in total melanomas is indicative of role for Parkinson's disease and its treatment, as the two populations differed primarily on this factor, it is difficult to explain physiologically how this would predispose one to in situ but not invasive melanomas. One potential explanation for this is that subjects volunteering for the free community screening offered by the AAD may have been more likely to lack regular access to health care, and hence may have had an unusually high number of invasive melanomas at screening. This would be expected to reduce the ratio of invasive melanomas as compared to EP002. A similar pattern was

seen when the number of melanomas in the rasagiline development program (observed melanomas) was compared to the number of melanomas expected based on age- and gender-specific rates within the AAD screening program.

The preceding hypotheses on the discrepancy between in situ and invasive rates, although plausible, cannot be verified. This reviewer believes that the large incongruity in the elevation of melanoma rates by pathological subtype suggests that factors other than the presence of PD and its treatments are influencing melanoma progression or detection, undermining the conclusions that can be reached from the analysis. At best, the EP002/AAD comparison may suggest a role for PD and its treatment in the development of melanoma. It cannot, however, directly speak to a potential contributory role for rasagiline, as rasagiline treatment was not a part of either study.

11.1.3 Delayed Start Analysis

The FDA requested in the Approvable Letter that the sponsor provide case and exposure data comparing the number of melanomas observed throughout the various study phases (placebo/active-controlled, and open-label extension) for the two groups: 1) patients randomized to rasagiline from the start of the study, and 2) patients with a "delayed start" of rasagiline (i.e., subjects initially treated with placebo and later rasagiline).

When standardized to cases per 1,000 person-years exposure to rasagiline[92], the rate of total melanomas in the delayed start group (2/557.2 person-years, or 3.4 [95% C.I. 0.4, 13.0] melanomas per 1000 person-years rasagiline exposure) was approximately three-fold less than the rate of total melanomas within the immediate start group (15/1344.6, or 11.6 [95% C.I. 6.2, 18.4] melanomas per 1000 person-years). When the risk of melanoma is calculated for progressive time-periods from either the study start (exposure to rasagiline *or* placebo) or from time of first rasagiline exposure, the risk in most time periods is relatively similar for the immediate and delayed start groups in both the combined and individual studies. The exception was in the >24 month time period, which showed an approximately three-fold elevation in risk in the immediate start (1.0%, n=6) compared to the delayed start group (0.3%, n=1).

I believe this comparison is not particularly informative regarding the factors that may contribute to the elevation in the immediate start melanomas. Although there is a three-fold increase in the rate of melanoma per 100 PYs in the immediate start group, the confidence intervals for the immediate and delayed start group overlap considerably. This is likely reflective of the small number of cases, in particular in the delayed start group (n=2), and a resultant lack of robustness in the analysis. In addition, commencement of active screening for melanoma within the rasagiline development program, and the subsequent increase in melanoma detection due to an apparent surveillance bias, is a substantial confounder to the subanalyses of the development of melanomas as affected by time from study start

[92] Placebo time in the delayed start (or placebo-rasagiline) group was not included in the exposure time.

11.1.4 Other Findings Relevant to the Melanoma Evaluation

Teva reported that[93], as per study protocol, the evaluation of lesions biopsied during dermatologic screenings was initially performed by a local laboratory, followed by a definitive diagnosis made by a central laboratory. The sponsor stated for 14 out of 751 total biopsies[94] there was a discrepancy between the diagnosis made by the central and the local laboratory: in four cases the local laboratory classified the lesion as a nevus, with the central laboratory revising the diagnosis to a melanoma, and in ten cases the local laboratory designation of a melanoma was revised to a less advanced lesion by the central laboratory (Exact binomial, P [10; 0.5, 14] = 0.06). A review of the literature on inter-rater reliability in the pathologic diagnosis of melanomas, conducted by a FDA consultant within the Division of Dermatologic and Dental Drug Products, provided evidence that this degree of discrepancy would not be unexpected due to the inherent difficulties in the clinical recognition of melanomas.

11.1.5 Reviewer Recommendations on Melanoma

The safety analysis to date has attempted to compensate for the lack of a control group for melanomas in the rasagiline development program through multiple analyses addressing questions indirectly related to a potential relationship between melanomas and rasagiline exposure. Some of these analyses have been supportive of a role for rasagiline and melanoma development, and some have not. Because it is not possible to know the exact applicability and respective weight that should be assigned to these various surrogate analyses, it is difficult to assess the totality of the data to reach a final conclusion. Although other manipulations of the current data are possible, the highest yield analyses have essentially been exhausted. I therefore now believe that these analyses and any further analyses of the data at hand will not further elucidate the safety of rasagiline with respect to melanoma.

For these reasons, I recommend that a large simple study, such as the requested Phase IV study described in the Approvable Action letter, be conducted to provide a more definitive understanding of the potential role of rasagiline in melanoma development. Furthermore, in light of the above conclusion that existing data cannot provide a satisfactory conclusion on the matter, this study should be conducted ***prior*** *to drug approvable, as opposed to Phase IV as described in the Approvable Action letter. The recommendation for completing a melanoma study prior to approval is strengthened by the pre-clinical findings regarding melanoma and rasagiline, which included:*

[93] In the sponsor's response to the FDA request for increased attribution of discontinuations due to adverse event (Section 7 of this review), the sponsor described an adverse event in which a subject's dermatologic biopsy was initially read as melanoma in situ by a local laboratory, and then designated as a nevus as per the central laboratory reading. This prompted an enquiry to the sponsor asking for how many other subjects the pathology assessments of the local and central laboratories were different with respect to their conclusion on the presence of melanoma.
[94] Biopsies completed through the end of August 2004.

- *The rare occurrence of a melanoma in one rasagiline-treated albino rat out of approximately 60 rats dosed (Background rate of melanomas in albino rats estimated at 0.14%)*
- *An association between rasagiline treatment and lung cancer in mice*
- *Evidence of rasagiline genotoxicity in three separate assays*

11.2 ECG

In the original NDA review, the sponsor's analysis of ECGs in the monotherapy cohort (study TEMPO) was inadequate: ECGs were only classified as "normal" or "abnormal", without collecting data on the nature of the abnormality or interval measurement. The Approvable Action Letter therefore requested that the ECGs from TEMPO be centrally re-read and analyzed in a manner similar to the more detailed analysis of ECGs in the adjunctive therapy cohort (studies PRESTO and LARGO).

The sponsor submitted the requested data as well as an overall assessment in conjunction with prior ECG data from the adjunctive studies PRESTO and LARGO. Measurements of QT interval prolongation were overall equivalent or less with rasagiline treatment than with placebo, for both the newly analyzed monotherapy subjects and the adjunctive therapy subjects. Although the ECG data collection and analysis performed by the sponsor could be improved in some regards (such as taking multiple baseline measurements and recording information on ECG timing with respect to last study dose), the overall quality and quantity of the data, in combination with results noted immediately above, do not necessitate that additional studies be performed at this time. However, should the drug be approved, it will still need to be determined if a "thorough" ECG study should be conducted as a phase IV commitment given the requirements of the newly finalized ICH E14 guidance.

11.3 Flu Syndrome

Flu syndrome and musculoskeletal adverse events were commonly reported in the rasagiline development program, and as the sponsor did not provide significant analysis or commentary on this issue within the original NDA, the DNDP requested that they explore the issue more thoroughly.

In their subsequent additional analyses (submitted with the response to the Approvable Letter), the sponsor addressed the following:

- Most of these events were reported independently, which the sponsor clarified as meaning they were not reported in conjunction with each other or with "flu syndrome."
- Occurrence of flu syndrome did not seem to be influenced by concomitant use of amantadine. For monotherapy subjects, anticholinergics were the only concomitant anti-Parkinson's disease medications allowed by protocol, and only two subjects were found to have received amantadine. For adjunctive therapy subjects, the sponsor

noted that approximately 25% of both treatment groups received amantadine. Teva stated that no rasagiline- or placebo-treated patients also receiving amantadine developed flu syndrome. However, for the 75% of subjects *not* receiving amantadine, the incidence of flu syndrome was 1.4% (4 subjects) in the rasagiline 1 mg group compared to 0.7% (2 subjects) in the placebo group.

- Teva noted that no subject reported recurrent bouts of flu syndrome, and most monotherapy patients reporting flu did so during the expected flu "season."
- The adverse events examined did not demonstrate a clear dose-response relationship, and elevations of some of the adverse events were not observed for all rasagiline dose groups.
- The sponsor stated that other Parkinson's disease therapies (ropinirole) have also demonstrated an excess of flu syndrome and related adverse events in the treatment group.

The sponsor concluded that there was no readily apparent explanation for the increased incidence of flu syndrome within some rasagiline treatment groups, but maintained that the data does not support a causal role for rasagiline or the existence of a flu syndrome. The sponsor did state that the possibility of arthralgia as a drug effect could not be excluded. I generally agree with the sponsor's assessment, but the issue warrants follow-up during post-marketing if rasagiline receives approval.

11.4 Blood Pressure

The FDA Approvable Action Letter asked that the sponsor characterize changes in blood pressure timed to dosing, ideally capturing the effect at T_{max}, as well as at other appropriate times during the dosing interval. The request noted that such data was not collected in the pivotal trials. In response, Teva cited pooled data from six Phase 1 studies (encompassing a total of 76-rasagiline treated healthy subjects) as an apparent substitute for the Approvable Letter request. Although the studies did not demonstrate a significant risk of hypotensive events, these data do not suffice as a replacement for the data requested in the Approvable Letter. The reasons for this include that one third of the studies (two of the six total) lacked placebo control, and a single study of uniform design and dosing would be preferable to pooled studies of differing doses and protocol. In addition, these studies were conducted in healthy volunteers, and not in Parkinson's disease patients who may be more susceptible to a potential hypotensive effect for rasagiline.

The sponsor is therefore requested to collect the additional data as specified in the Approvable Action Letter. Given that the sponsor has provided some partial data in support of the hemodynamic safety of rasagiline in the form of the Phase I studies, I believe it is acceptable for this study to be performed during the Phase IV period if rasagiline receives approval.

11.5 Missing Adverse Event Attribution

For approximately 7% of discontinuations in the rasagiline development program, the discontinuation was not attributed to a specific AE. The sponsor was therefore requested in the Approvable Letter to take additional measures to identify the AEs associated with discontinuation for a particular subject. The sponsor did attribute specific AEs (syncope, rash, extrapyramidal syndrome, dizziness, hypertension, vascular disorder and melanoma [n=2]) for eight of the ten subjects lacking specific adverse events, and explained that two of ten had been incorrectly included among subjects discontinuing due to AE. These newly attributed AEs did not change the ranking of commonly occurring AEs within the development program.

11.6 Laboratory Data Analysis

In the Approvable Action letter, the DNDP requested the laboratory and vital sign data be reassessed as mean change from baseline to the subject's *Maximal* Observed Value, as opposed to Last Observed Value (LOV), as was done in the original NDA submission. No significant changes in laboratory parameters were observed with this re-analysis. Slight increases in some hemodynamic parameters, most notably in supine minus standing SBP and DBP, were observed when the vital sign data was re-analyzed as change to Maximal Observed Value. However, the absolute changes were small and no new patterns among doses were observed in comparison to the prior analysis.

11.7 Postmarketing Rhabdomyolysis Surveillance

Although the DNDP did not consider the two confounded cases of rhabdomyolysis within the rasagiline development program to constitute a significant safety signal, Teva was asked to be vigilant in its postmarketing surveillance. Teva submitted criteria for the identification of such cases.[95] These criteria were generally acceptable with the exception that the criterion of a 10-fold CPK elevation from baseline should be reduced to a 5-fold CPK elevation. This reduction is recommended to avoid the loss of potential cases that may be excluded by the higher threshold.

11.8 Concomitant Antidepressant Use with Rasagiline

The sponsor has provided data documenting the lack of apparent serotonin syndrome cases within the rasagiline development program, as well as data suggesting that serious adverse events are not strongly associated with concomitant antidepressant and rasagiline usage. However, the sponsor acknowledges that the overall exposure to these antidepressants was limited in the rasagiline development program with regards to the number exposed. This reviewer would also add that the exposure in the rasagiline

[95] These criteria are provided on page 66 of this review.

development program was inadequate in regards to antidepressant dose, in light of what patients may receive concomitantly in regular clinical treatment with antidepressants.

Given this lack of adequate exposure, coupled with rare but potentially fatal case reports of serotonin syndrome in another MAO inhibitor used in the treatment of Parkinson's disease (selegiline), I recommend that the language within the FDA proposed labeling (see Attachment 12.1 of this review) be maintained, and that placement in the WARNINGS section is appropriate. Upon review of the above sponsor data I would now recommend the addition of:

- Further language clearly advising physicians that the antidepressant doses on which labeling data was based were lower than those frequently used in the treatment of depression should be inserted. The proposed labeling sent with the Approvable Letter notes the small number of subjects exposed, but does not stress the restricted doses.
- A stronger caution against co-administration of antidepressants that were excluded from the rasagiline development program due to prior serious reactions with other MAOIs, such as fluoxetine and fluvoxamine, as well as those for which only single digit subject exposures occurred in the development program, such as venlafaxine.

If rasagiline receives FDA approval, this issue should receive close monitoring in the post-marketing period.

11.9 Sponsor Safety Update

The sponsor provided a summary of the safety data accumulated since the time of the last update. This most recent data did not demonstrate any substantial changes in deaths, adverse events, discontinuations or other safety relevant issues from prior updates and reviews.

11.10 Worldwide Regulatory Update

In addition to the requested safety data, the sponsor was also asked to provide a summary of the current worldwide regulatory action pertaining to rasagiline. As discussed in Section 1.4 of this review, the synopsis of actions from other regulatory agencies were notable for their range of conclusions regarding the causality and implications of the high relative incidence of melanomas. Specifically, conclusions ranged from the opinion that the data are inconsistent with a causal relationship between melanoma and rasagiline treatment (, to requiring extensive preclinical studies demonstrating a lack of carcinogenicity before consideration of human data could proceed). Rasagiline has been approved for marketing in the European Union and Israel. Safety related labeling recommendations for rasagiline from the DNDP Approvable Letter[96] are included in Attachment 12.1 of this review.

[96] Updated DNDP Safety Team recommendations for safety labeling will be provided in a separate FDA document should rasagiline be approved.

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Attachment 12.2: Case Characteristics for the 24 Melanomas Diagnosed During the Rasagiline Development Program

(Adapted from Sponsor Table 1, Response to FDA Data Request, Received via e-mail February 1, 2005)

	Patient No.	Study	Melanoma Type	Dose at Diagnosis
1.	164	232	Invasive	2 mg
2.	113	232	In situ	2 mg
3.	246	233	In situ	2 mg
4.	9	233	Invasive	1 mg
5.	64	233	In situ	1 mg
6.			Invasive	1 mg
7.	36	233	In situ	1 mg
8.	209	133	Invasive	0.5 mg
9.	520	135	In situ	1 mg
10.	494	135	In situ	1 mg
11.	116	233	In situ	1 mg
12.	613	133	In situ	1 mg
13.	424	135	Invasive	1 mg
14.	169	133	Invasive	1 mg
15.	544	233	Invasive	1 mg
16.	271	135	Invasive	0.5 mg
17.	118	233	Invasive	1 mg
18.	72	233	In situ	1 mg
19.	1012	113	In situ	1 mg
20.			In situ	1 mg
21.	41604	122	In situ	Placebo
22.	16431	122	Invasive	Before treatment initiation
23.	141611	122	In situ	Before treatment initiation
24.	756	133	In situ	Before treatment initiation

Study Numbers: 232 = Monotherapy Study TEMPO; 233 = Open-Label Extension of Monotherapy Study TEMPO; 133 = Adjunctive Therapy Study PRESTO; 135 = Open-Label Extension of Adjunctive Study PRESTO; 113 = TVP-1012/113, an open-label extension of a placebo-controlled trial (TVP-1012/112) in levodopa-treated PD patients receiving 0.5 mg rasagiline, 1.0 mg rasagiline or placebo for 12 weeks. Studies 112/113 were conducted in Hungary and Israel.

Attachment 12.3: Summary of Sponsor North American Cohort Study EP002

(Taken from Sponsor EP002 Final Study Report Synopsis, 120 Day Safety Update, CTD Section 5.3.5.4.3 EP002. Report dated December 15, 2003)

Objectives

The purpose of this cohort study is to assess the prevalence of melanoma, basal cell carcinoma, squamous cell carcinoma, and additional neoplasms in PD patients when proactive screening dermatology exams are implemented. This cohort study is part of a comprehensive epidemiological program designed to collect sufficient reference data on the incidence of malignant melanoma and compare it to that observed in the rasagiline clinical trials program. Additionally, this cohort study should provide information on the effect of proactive dermatological screening on the prevalence rates, give support in assessing the influence of PD on melanoma risk, and provide an estimate of the invasive/in-situ melanoma ratio in proactive screening programs

Methodology

In this epidemiological cohort study, patients with an established diagnosis of PD were evaluated for their medical history, including previous skin disorders and melanoma risk factors according to a pre-defined questionnaire.

The study consisted of two separate visits, one to the neurologist and one to the dermatologist. The neurologist was responsible for recruiting patients with an established diagnosis of PD, obtaining informed consent, recording demography, obtaining medical history, and recording concomitant medications. Since patients with a previously documented diagnosis of PD were chosen to participate in the study, a general physical and neurological examination were not performed. The dermatologist performed a complete dermatological examination, recorded the patients. Dermatological history including risk factors for melanoma, and biopsied any suspected cancerous lesions including, but not limited to, malignant melanoma, basal cell carcinoma, and squamous cell carcinoma. Any suspicious lesion was considered for a biopsy, at the discretion of the dermatologist. Slides of all biopsy specimens were evaluated by a central dermatopathologist to establish the diagnosis.

Number of Patients

A total of 2106 PD patients from multiple study sites in Canada and the USA completed the study.

Diagnosis and Main Criteria for Inclusion

Adults with a confirmed diagnosis of Parkinson's Disease. Patients not previously exposed to Teva's experimental drug rasagiline (TVP-1012). Patients must be willing and able to give informed consent. Patients must not be taking any investigational drug at the time of enrollment.

Duration of Study

This study consisted of two separate visits. The first patient enrolled on January 13, 2003. The last patient completed study on September 7, 2003.

Criteria for Evaluation

The prevalence and incidence of melanoma as well as the prevalence of basal cell carcinoma, squamous cell carcinoma and additional neoplasms were evaluated.

Statistical Considerations

The statistical presentation for this study is descriptive only. Continuous variables are presented as mean, standard deviation, median, minimum and maximum values. Categorical parameters are presented in contingency tables including frequency counts and percentages.

Results

The majority of the 2106 PD patients who completed the study were males (68.2%), Caucasian (92.9%), greater than 65 years of age (65.7%), and had never used tobacco (57.0%)

On entry into the study, patients had been diagnosed with PD for a mean 7.1 years (range: 0 to 48 years). Most of the patients (82.8%) had PD severity that ranged from 2.0 to 3.0 on the Hoehn and Yahr 5-point staging scale; mean severity was 2.2. The PD population included in this cohort study, when adjusted for the proportions of patients with motor fluctuating PD and those with early PD diagnosis, is comparable with that observed in the rasagiline clinical trials program. A review of the past or current medications taken by the patients showed that 96.6% of the patients took dopaminergic agents and 13.0% of the patients took anti-muscarinic agents to treat their PD. The most commonly used dopaminergic agents were: levodopa/levodopa modified-release (92.4%); pramipexole (33.4%); amantadine hydrochloride (21.2%); entacapone (19.2%); ropinirole hydrochloride (16.9%); and selegiline hydrochloride (15.1%). The majority of the patients (85.0%) had at least one melanoma risk factor detected. Two or more melanoma risk factors were identified in 69.2% patients and the mean number of melanoma risk factors was 3.0 (range: 0 to 11).

The five most frequent melanoma risk factors detected in this patient population were: fair complexion (56.9%); blue eyes (42.0%); severe or blistering sunburns in childhood

(40.9%); sun sensitivity (33.5%); and freckles (25.4%). In this PD population, 73 (3.5%) patients had a personal history of melanoma.

During the dermatological examinations, 519 (24.6%) patients had suspicious skin lesions and 346 (16.4%) had suspicious pigmented lesions. Of these patients, 392 (18.6%) patients underwent biopsies. Twenty-four patients (1.1%) were diagnosed with melanoma; 20 (0.9%) patients had in-situ melanoma and 4 (0.2%) patients had invasive melanoma. Basal cell carcinoma and squamous cell carcinoma were detected in 86 (4.1%) patients and in 22 (1.0%) patients, respectively.

A total of 97 melanoma cases were recorded either in the patient's medical history or diagnosed by the dermatological examinations during this cohort study; 26 cases of invasive melanoma, 59 cases of melanoma in situ cases, and 12 cases of unclassified melanoma. An estimated invasive to in situ melanoma ratio is 1:2.3, indicating that melanoma in situ occurs more frequently than invasive melanoma. During the dermatological examinations 24 cases of melanoma were detected; 20 cases of melanoma in situ and 4 cases of invasive melanoma indicating a prevalence of 0.9% for melanoma in situ and a prevalence of 0.2% for invasive melanoma.

The total prevalence of melanoma observed in this cohort study is 1.1%, 18.3 times higher than that reported in SEER registries during 1999 in the USA. The prevalence ratio of invasive to in situ melanoma is 1:5.0. This suggests that proactive screening, as conducted in this cohort study and in the rasagiline clinical trials program, is more prone to identify higher numbers of in situ melanoma cases due to the elimination of the lead-time detection bias caused by conversion of in situ cases to invasive melanoma. The ratio of observed to expected melanomas cases indicated that the incidence of melanoma in this cohort study in PD patients is 6.9 times higher than in a comparable age and sex matched population.

The principal analysis using pooled data from this study and other similar studies compared melanoma risk estimates to those observed in the ongoing rasagiline clinical development program. The incidence rate of melanoma in the ongoing investigational drug program was determined prospectively. While in this study and other similar studies, the incidence rate of melanoma was determined retrospectively using the retrospective evaluation approach and combining the total number of melanoma cases in the two years prior to study and the melanoma cases diagnosed during the study.

Sponsor Conclusion

The data emerging from this cohort study may suggest that a proactive dermatological screening as done in this cohort study and in the rasagiline clinical trials program is associated with an increased incidence of melanoma reporting and a possible increased risk of melanoma in PD patients.

Attachment 12.4: American Academy of Dermatology (AAD) Screening Program Overview

(Adapted from Geller et al. The first 15 years of the American Academy of Dermatology Skin Cancer Screening Programs: 1985-1999. Cancer 2002;95:1554-61)

Objectives

The American Academy of Dermatology (AAD) Skin Cancer Screening Program was conducted to:

- Investigate the efficacy and cost-effectiveness of skin cancer screening
- Collect skin cancer prevalence statistics
- Identify skin cancer risk factors and population sub-groups at particular risk
- Provide large-scale screenings to the general public as a public health service

Methods

The AAD Screening Program consisted of community-based screenings open to the public, publicized in the local media and performed by volunteer dermatologists. Screenings were conducted throughout the fifty states and Washington, DC. Prior to the screenings, information on participant demographics, access to dermatologic and other medical care, and melanoma risk factors (including a personal or family history of skin cancer) was collected via a standardized form. The dermatologists performing the screenings did not perform biopsies, but participants were informed of presumptive diagnoses made during the screening. For a three-year period (1992-1994), subjects with lesions suspicious for melanomas were sent letters requesting follow-up information asking whether they had seen a physician for biopsy and/or treatment of the lesion and, if so, to provide the name of that physician. After obtaining the name of the treating physician, confirmatory pathology reports on both the initial biopsy and subsequent re-excisions were requested from these physicians. The researchers were able to contact approximately 96% of screenees with suspicious lesions, and obtained a confirmatory diagnosis for 72%.

Results

Since commencing in 1986, the AAD Skin Cancer Screening Program has performed approximately 1.2 million screenings in 1 million patients. In the pre-screening questionnaires, about 15% of subjects indicated that they had participated in a previous AAD screening.

Of the 242,374 screenings during which a presumptive diagnosis was made, more than 10 percent of participants were suspected of having skin cancer: approximately 9% basal cell carcinoma, 1% squamous cell carcinoma, and 0.8% melanoma. Upon further examination of the suspected melanoma lesions, approximately 20% were confirmed by

biopsy (363 confirmed melanomas out of 1938 lesions suspicious for melanoma). The large majority of these melanomas (greater than 90%) were discovered at an early stage of development, either in situ or less than 1.5 mm in thickness.

Reviewer comment: *I was unable to find the percentage of invasive to in situ melanomas within the literature reports describing the AAD screening program. However, based upon the numbers provided in Attachment 12.5 of this review (AAD Melanoma Rates, 1992-1994, Biopsy-Confirmed Melanomas Among All Persons Screened), 73% of melanomas were invasive and 27% were in situ. As discussed in Section 2.2.7 of this review, this ratio may reflect an increased propensity for invasive melanomas within the AAD screening population.*

Forty four (44) percent of individuals diagnosed with melanoma were white men over the age of 50, although this subgroup comprised less than 20 percent of all those screened during the three-year time period from 1992 to 1994. The greatest predictive value (32%) for melanoma screening was found for men age over 50 years with a changing mole and skin type I or II.

The majority of AAD participants had one or more risk factors for developing skin cancer: 95% were white, 37% had a fair complexion and sunburn easily, 33% had a family history of a changing mole, and 28% had a family history of skin cancer.

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Attachment 12.5: AAD Melanoma Rates, 1992-1994, Biopsy-Confirmed Melanomas Among All Persons Screened

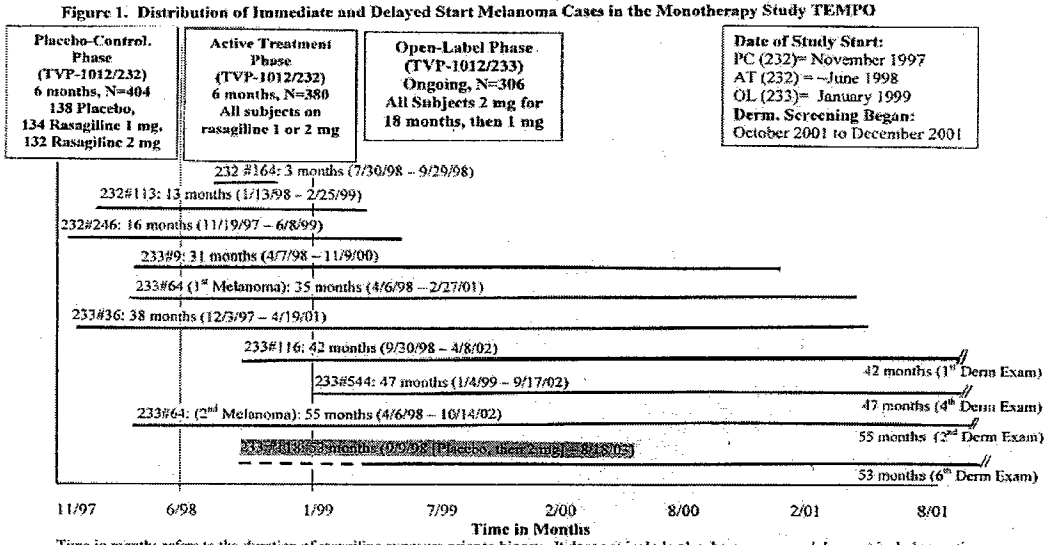
	Invasive Melanoma						In Situ Melanoma					
	Men			Women			Men			Women		
	Case	Screened	Rate*	Case	Screened	Rate*	Case	Screened	Rate*	Case	Screened	Rate*
<45	19	26537	71.6	30	51253	58.5	6	26537	22.6	7	51253	13.7
45-54	29	16455	176.2	19	26192	72.5	13	16455	79.0	13	26192	49.6
55-64	34	19952	170.4	20	27837	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.

Attachment 12.6: Melanoma Delayed Versus Immediate Start Figures

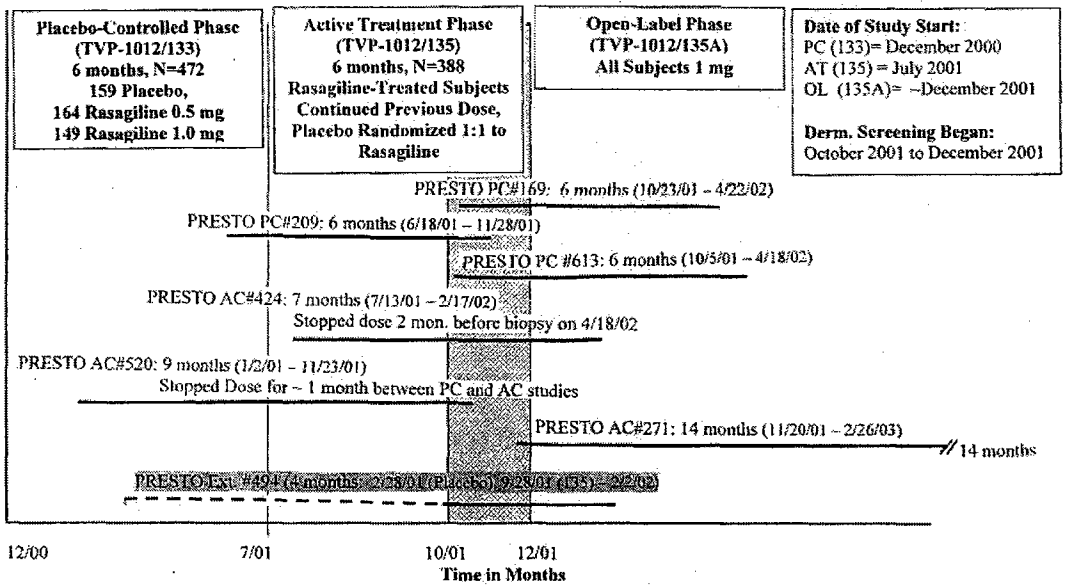
(Prepared for the DNDP presentation of rasagiline melanoma data at the FDA Epidemiology Forum on May 5, 2005)

Figure 1. Distribution of Immediate and Delayed Start Melanoma Cases in the Monotherapy Study TEMPO



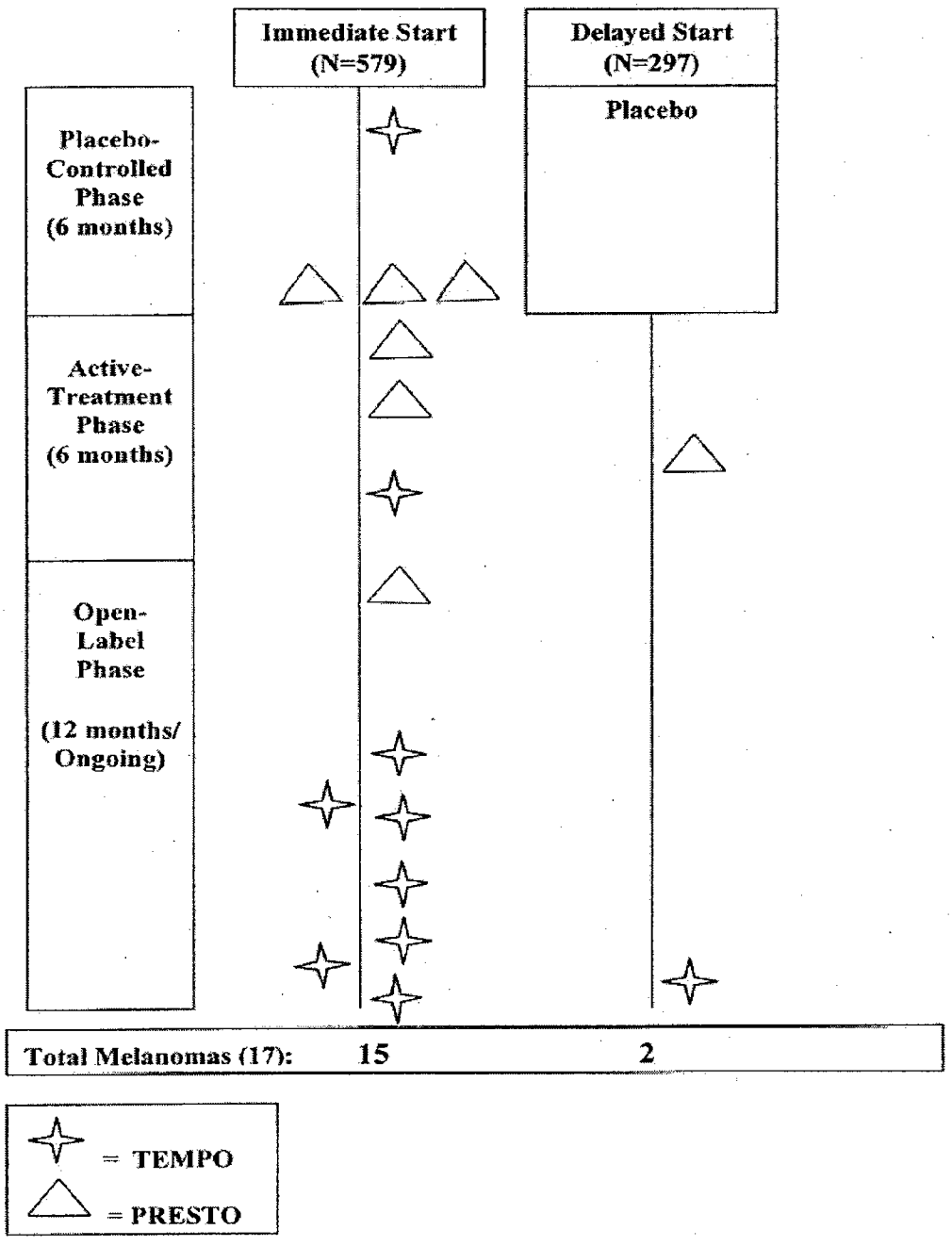
Time in months refers to the duration of rasagiline exposure prior to biopsy. It does not include placebo exposure and does not include any time between prior discontinuation of rasagiline and a subsequent biopsy. The end date generally corresponds to the date of the diagnosis biopsy.

Figure 2. Distribution of Immediate and Delayed Start Melanoma Cases in the LD Adjunctive Study PRESTO



Time in months refers to the duration of rasagiline exposure prior to biopsy. It does not include placebo exposure and does not include any time between prior discontinuation of rasagiline and a subsequent biopsy. The end date generally corresponds to the date of the diagnosis biopsy.

Figure 3. Distribution of the Diagnosis of Melanoma Cases within the Delayed and Immediate Start Treatment Groups of the Combined TEMPO and PRESTO Studies, As Measured in Months from the Subjects' First Study Dose (Note: Time Not to Scale)



Attachment 12.7: Narratives for Subjects with Abnormal ECG Results
(Adapted from the respective sponsor study reports)

Narratives for TEMPO Patients

TEMPO: Rasagiline 1 mg

- **TVP-1012/232 #555**, a 60 year old female on rasagiline 1 mg had a history of hypothyroidism and diabetes mellitus. Concomitant medications included guaiphenesin, thyroxine sodium, multivitamins, ginkgo biloba, conjugated estrogens, alendronic acid, fexofenadine hydrochloride, fluticasone propionate and vitamin E.

  ECG results were:

Visit	ECG Results
Screening (30 Nov 98)	QTcB 389 msec, QTcF 388 msec
Week 14 (31 Mar 99)	QTcB 430 msec, QTcF 418 msec
Termination (22 Jun 99)	QTcB 450 msec, QTcF 429 msec (Change in QTcB > 60 msec)

  She withdrew from the extension study (TVP-1012/233) at her request in September, 2000, after 1.7 years of rasagiline exposure. No cardiovascular AEs were reported. A few mild AEs of lightheadedness/dizziness were reported during rasagiline treatment.

Two additional patients treated with rasagiline 1 mg during the placebo-controlled phase of the TEMPO study appear on the PCS list for QTcB (both had change in QTcB between 30 and 60 msec) and also had a cardiovascular SAE reported during this phase:

- **TVP-1012/232 #286** had QTcB of 404 msec at screening (April 29, 1998) which increased to 429 and 444 msec at Week 14 (August 27, 1998) and termination (November 30, 1998) visits (of the placebo-controlled phase), respectively. The patient entered the study with a history of atypical angina (since 1996) and experienced the SAE of a coronary artery bypass surgery (—); he continued the study drug uneventfully. As of the time of the sponsor narrative, he had 5.7 years of exposure to rasagiline.

- **TVP-1012/232 #616** had QTcB of 407 msec at screening which increased to 437 and 443 msec at subsequent visits. He was noted to be in new onset atrial fibrillation at the termination visit of the placebo-controlled phase. He continued the study with 5.2 years of exposure to rasagiline as of this report.

TEMPO: Rasagiline 2 mg

- **TVP-1012/232 #77**, a 74 year old male on rasagiline 2 mg had a history of coronary artery bypass graft (1988), hypertension, diabetes and hypercholesterolemia.

Concomitant medications included aspirin, atenolol, dipyridamole, lovastatin, loratadine, lisinopril, tramadol, benzhexol and doxycycline.

ECG results were:

Visit	ECG Results
Screening (19 Dec 97)	Sinus bradycardia 47 bpm, first degree AVB, inverted T waves; QTcB 331 msec, QTcF 345 msec.
Week 14 (26 Mar 98)	Sinus bradycardia 44 bpm, first degree AVB, inverted T waves; QTcB 370 msec, QTcF 389 msec
Termination (22 Jun 98)	Sinus bradycardia 47 bpm, inverted T waves. QTcB 405 msec, QTcF 421 msec. (Change in QTcB and QTcF > 60 msec)

He completed the study according to protocol and as of this report had an ongoing total exposure to rasagiline of six years. No cardiovascular AEs were reported while on rasagiline. Hyperglycemia and elevated urea nitrogen and creatinine were noted on March 26 1998, but had resolved by May 7 1998.

- **TVP-1012/232 # 614**, a 50 year old female had a history of palpitations (in the past), tension headache, dizzy spells (in the past) and chronic corneal erosions. Concomitant medications included oestradiol and celecoxib.

ECG results were:

Visit	ECG Results
Screening (31 Mar 99)	QTcB 375 msec, QTcF 379 msec
Week 14 (12 Jul 99)	QTcB 400 msec, QTcF 393 msec
Termination (4 Oct 99)	QTcB 441 msec, QTcF 427 msec (change in QTcB > 60 msec)

She was exposed to rasagiline for 4.8 years. No cardiovascular AEs were reported during the core study. On October 27, 2003, moderate AE of "irregular heartbeat" was reported after 4.6 years on rasagiline. No changes in the study drug occurred and the patient is still in the study.

As was already reported in Section 5.4.1.4 of the 120-day update, a case of QT interval prolongation (patient # 7 on rasagiline 2 mg) was reported as an AE at the termination visit of the placebo-controlled phase of the TEMPO study. All ECG recordings of this patient were reviewed and interpreted by two cardiologists, Drs. —
They concluded that there was no evidence for QT prolongation. Relevant documentation was provided in Appendix 16.2.1.9.4 of the TEMPO clinical study report (CTD Section 5.3.5.1.1).

Narratives for PRESTO Patients

PRESTO: Rasagiline 0.5 mg

- **TVP-1012/133 #253.** This 55 year old male had a history of myocardial infarction and stent placement (2000), intermittent hypertension (since 2000), peripheral vascular disease (since 2001), venous insufficiency, bilateral leg ulcers secondary to vein stasis, edema of lower extremities, gastric ulcer, constipation, osteoarthritis, asthma, and depression. Concomitant medications included LD/CD, pramipexole, furosemide, potassium supplement, atenonol, aspirin, metolazone, and vitamin C.

  ECG results were:

Visit	ECG Results
Screening (26 Mar 2002)	LAH. Depressed ST segment and flat T waves, QTcB 454 msec, QTcF 437 msec
Termination (4 Sep 2002)	Artificial pacemaker rhythm. QTcB 527 msec, QTcF 510 msec. (PCS absolute QTcB and QTcF > 500 msec) (Change in QTcB > 60 msec, Change in QTcF >60 msec)

  Potassium was 3.6 mmol/L at screening, 3.0 mmol/L at baseline (May 1 2002) and 3.4 mmol/L at termination. Chest X-ray showed borderline cardiomegaly with left ventricular prominence. On [redacted] the patient was admitted to the hospital for ventricular tachycardia. Vital signs were within normal range. He discontinued the study drug on [redacted] Termination ECG was recorded 2 months after discontinuation of the study drug and showed artificial pacemaker rhythm. On [redacted] the subject was admitted to a psychiatric facility for treatment of moderate gambling addiction.

Narratives for LARGO Patients

LARGO: Rasagiline 1 mg

- **TVP-1012/122 #15607:** This 52 year old female had a history of chronic cerebral vascular insufficiency and hypercholesterolemia. Concomitant medications were LD/CD and amantadine.

  ECG results were:

Visit	ECG Results
Screening (05 Mar 2002)	Normal, QTcB 360 msec, QTcF 362 msec.
Termination (30 Jul 02)	Normal, QTcB 424msec, QTcF 409 msec. (Change in QTcB > 60 msec)

  No adverse events were recorded. Cholesterol was elevated during the entire study. No PCS vital signs measurements were recorded.

- **TVP-1012/122 #16211:** This 74 year old female had a history of varicose veins of the legs, refraction disorder, LBBB on ECG (since 1996), osteoporosis and chronic

erysipelas. Concomitant medications were LD/BZ, LD/CD, alendronic acid, amantadine, bromocriptine, calcium, Vitamin D, and penicillin G.

ECG results were:

Visit	ECG Results
Screening (19 Nov 2001)	First degree AVB, LBBB, QTcB 457 msec, QTcF 444 msec.
Termination (22 May 02)	First degree AVB, LBBB, QTcB 513 msec QTcF 494 msec. (Absolute QTcB > 500 msec) (Change in QTcB > 60 msec)

No cardiovascular adverse events were recorded. No PCS vital signs or relevant laboratory abnormalities were noted.

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Attachment 12.8: Narratives for Subjects Experiencing MIs during the Placebo-Controlled Portions of the Three Pivotal Studies (PRESTO, LARGO and TEMPO)
(Adapted from the respective Sponsor Study Reports)

1. **Monotherapy Study TEMPO (TVP-1012/232) #179** was a 72 year old man who discontinued 1 mg/day rasagiline on ~ , 49 days after study entry, due to elective surgery for an abdominal aortic aneurysm and myocardial infarct. He had a medical history including atrial fibrillation from 1992, bilateral carotid stenosis, hypertension from 1991, amaurosis fugax in 1992 and abdominal aortic aneurysm from 1995. His concomitant medications included verapamil, digoxin and warfarin.

   In ~ he was admitted for elective surgical repair of an abdominal aortic aneurysm present since 1995. The patient suffered a cardiac arrest leading to myocardial infarction (requiring a coronary by-pass graft) and deep vein thrombosis during surgery. At the time of the report, the patient still had a residual foot drop and toe tip necrosis as a result of lower extremity ischemia. Teva stated that the patient discontinued participation in the study because he was not ambulatory (TEMPO Study Report, pg. 125).

2. **Monotherapy Study TEMPO (TVP-1012/232) #249:** This 47 year old man started TVP-1012/232 in October 1998 and was assigned to the 2 mg rasagiline treatment. The patient with a history of hypercholesterolemia was hospitalized in ~ for a severe myocardial infarction. The infarct required TPA reperfusion followed by a four-vessel coronary artery bypass graft. The patient remained on study medication throughout the event.

3. **Adjunctive Therapy Study LARGO (TVP-1012/122) # 90112** was an 87 year old man receiving rasagiline 1 mg/day. His pre-study medical history was significant for left inguinal hernia repair (1996). His concomitant medications were lactulose, and levodopa/carbidopa.

   On February 4, 2002 subject took the last dose of study medication as per the protocol. That day, during the termination visit of the placebo-controlled phase, the subject underwent an ECG exam which indicated first degree A-V block, left atrial hypertrophy and Q-waves at V_1-V_3 suggestive of a septal myocardial infarction. These findings were not seen on the screening ECG which was normal. The subject had not experienced any cardiac symptoms during the core study period and it was felt at that time that the ECG changes may reflect lead placement artifact. The subject was therefore included in the extension phase. On February 5, 2002 (during the ext. phase) the subject's levodopa dose was raised from 600 mg daily to 800 mg daily and

later to 1000 mg daily. The subject was prescribed acetylsalicylic acid and furosemide as cardiovascular prophylaxis. An ECG performed at the termination visit of the extension phase revealed the same abnormalities described above, although the subject still denied having any cardiac symptoms at any time during the study. The sponsor concluded that the subject had probably suffered an earlier, subclinical myocardial infarction.

4. **LARGO (Adjunctive Therapy) # 50506:** This 68 year old man (rasagiline 1 mg/day) underwent two ECGs prior to receiving the study drug: the first read as demonstrating septal infarction and the second not. Teva stated that the subject's termination ECG was considered to have evidence of a "new" infarction in comparison to the second pre-drug tracing (LARGO Study Report, pg. 162).

5. **LARGO (Adjunctive Therapy) # 141401**: This 72 year old woman died after experiencing an acute myocardial infarction prior to randomization (LARGO Study Report, pg. 143).

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