

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-641

MEDICAL REVIEW(S)

Memorandum

To: File: NDA 21-641 (rasagiline, Teva)
From: Director Office of Drug Evaluation 1
Date: May 16, 2006
Subject: Memo to File (Rasagiline)

Dr. Katz' memo of May 14, 2006 recounts his resolution of the two principal concerns that led to our approvable letter on 8/4/05 potential for tyramine reactions and a possible signal for melanoma. As my memo of August 12, 2005 at the time of the 8/4/05 letter Rasagiline Memo2.doc (attached) discussed, I was skeptical about the association of melanoma and rasagiline, and I remain so (absence of clear dose-or duration-response; variable relation to delayed start or duration in TEMPO/PRESTO; epidemiologic evidence of increased melanoma in PD). Dr. Katz discusses fully those issues and the updated information assessed by Dr. Jones and concludes that the data "do not strongly suggest that R can cause or induce melanoma formation" although he cannot reach "reasonable certainty" that there is, or is not, an effect. In fact, the initial concern raised by the observation of more melanomas in the rasagiline database than in other development programs (5.8/1000 patient years vs 1.6 for the next highest pramipexole), an observation difficult to evaluate because of different levels of assessment, has not really been supported by any of the later analyses. Nonetheless, you cannot "prove a negative," and while I remain more skeptical than Dr. Katz and would conclude there really is little evidence, in a fairly substantial database, of an effect and that the initial concern is largely resolved, Teva's agreement to conduct a post-marketing LST to evaluate melanomas in the Parkinson's population will provide interesting epidemiologic data and greater assurance that there is indeed no problem.

Other issues have also been resolved. There will be a strong tyramine sensitivity warning until a proper tyranine sensitivity study is conducted post-marketing. Labeling also warns of additional class-associated interactions. Language on melanoma notes the apparent increase in rate of melanoma in PD generally and that there was not an apparent further increase related to rasagiline.

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

/s/

Robert Temple
5/16/2006 02:21:32 PM
MEDICAL OFFICER

MEMORANDUM

DATE: May 16, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-641

SUBJECT: Recommendation for action on NDA 21-641, for the use of Azilect (rasagiline mesylate) in the treatment of patients with Parkinson's Disease (PD)

NDA 21-641, for the use of Azilect (rasagiline mesylate) in the treatment of patients with Parkinson's Disease (PD), was submitted by TEVA Pharmaceuticals LTD on 9/5/03. The Agency has issued two Approvable (AE) letters; one on 7/2/04, and a second on 8/4/05. In the most recent AE letter, there were two critical issues that the sponsor was asked to address: a potential signal that rasagiline caused melanoma, and the potential for patients to experience hypertensive crises when ingesting a tyramine-rich meal. In addition to these issues, the sponsor was also asked to address several other issues, to be discussed below.

With regard to rasagiline's capacity to cause (or promote the development of) melanoma, the 8/4/05 AE letter described the Agency's concerns.

Specifically, we noted an increase in the tumor incidence between patients who had been enrolled in the immediate and delayed phases of the TEMPO study. In the TEMPO study, patients with early PD were randomized to receive drug or placebo (without concomitant l-dopa) for 6 months, after which patients who had originally received placebo were switched to drug while patients originally randomized to drug remained on drug. This was followed by a phase in which all patients received open-label rasagiline. In this study, it was noted that patients who had originally been randomized to rasagiline had a greater incidence of melanomas compared to those who had originally been randomized to placebo. The increased incidence was due to 6 tumors that appeared in the original drug group after 24 months of rasagiline exposure. Given that the placebo group had, at that time, on average about 6 months less exposure than the original drug group, this finding was consistent with the conclusion that longer time on drug was associated with increased tumor occurrence, a finding consistent with drug causation.

However, countering this finding was a finding from the PRESTO study (a study of similar design except it enrolled more advanced PD patients who were also receiving concomitant l-dopa). In this study, there was a similar increase in tumors in the Immediate start group, but in the first 2 months of exposure. Given that the delayed start group had a similar duration of exposure, the increase in

the immediate group could not be attributed to increased exposure. Therefore, the findings from the two studies was considered possibly related only to the variability in the data (and therefore raised serious questions about drug causality).

We also noted that the incidence of melanomas in the rasagiline development program was greater than that in the development programs of any of the recently approved PD treatments. Although it was true that after a few tumors (i.e., 6) were noted in the rasagiline program systematic monitoring was instituted in the clinical trials, and this did not occur in any of the other development programs, our conclusions about the comparative rates were based on the 6 tumors identified prior to the institution of this monitoring.

The letter also noted other findings that potentially exonerated the drug.

First, it appeared that there was no real evidence for tumor incidence to be related to dose. This finding was based on an analysis in which the dose at which a tumor was considered to have occurred was the patient's modal dose, and the denominator (Pt-yrs) was calculated by considering the actual amount of time a given patient received a given dose (that is, a given patient's experience could be included in multiple dose cells, if he or she received different doses at different times).

Second, the sponsor had submitted the results of Study EP002, in which PD patients who had not received rasagiline (but were on other PD treatments) were examined once for melanoma. The data from this study revealed an increase in tumor incidence several fold that seen in the American Academy of Dermatology (AAD) screening program, in which patients were also screened once for melanoma. This finding suggested that patients with PD had an increased incidence of melanomas compared to the general population. Although the circumstances of the AAD database were somewhat different than those of Study EP002 (for example, the AAD study was done about 10 years earlier, when tumor incidence was lower generally, and about 20% of the EP002 patients were from Canada, where tumor incidence is less than in the US), the findings were considered relatively strong. A Danish study reported in the literature also found an increase in melanomas in the PD population of about double that in the general population. The comparison of the rate of melanomas in the rasagiline database to the AAD study rate demonstrated an increase quantitatively very similar to that of the EP002/AAD comparison, suggesting that patients receiving rasagiline had a similar incidence of melanoma to those of PD patients not receiving rasagiline, although Dr. Jones expressed some reservations about this conclusion (the bulk of this increased risk was accounted for by an increase in in situ tumors, which she believed was possibly evidence of a bias in the comparison, related to the possibility of greater surveillance for tumors in the EP002 patients). Of course, assuming this increase in melanoma incidence in

PD patients is real, it is not known if it is due to the PD itself and/or to the drugs (including rasagiline) that these patients receive.

Finally, the letter noted an increase in the incidence of lung tumors in mice. Although the lowest dose that caused tumors produced an AUC that was about 170 times that seen at the exposures in humans at the effective dose, the NOEL for tumors produced an AUC that was only 5 times greater than the human AUC. The letter also noted that rasagiline is genotoxic in several assays.

In my memo of 8/4/05, I also noted that the dose response relationship (or lack thereof) was possibly an artifact of the fact that systematic screening for melanoma was instituted relatively late in the program, and that the small number of tumors seen in the 2 mg group (the high dose) was an artifact of the fact that there was relatively little time that patients were surveilled in this group, compared to the lower doses.

With regard to rasagiline's potential to cause hypertensive crises with the ingestion of tyramine containing foods, we noted that the sponsor had not adequately evaluated this potential. In the 8/4/05 AE letter, therefore, we gave the sponsor the option of performing an adequate tyramine-sensitivity study, or accepting language in product labeling that restricted dietary intake of these foods, with a commitment to perform an adequate study in Phase 4.

After the AE letter was sent, we met with the sponsor in 12/05 to discuss various aspects of the melanoma issue, after which they submitted responses to questions we asked at that meeting. Then, the sponsor ultimately submitted a complete response to the 8/4/05 AE letter on 3/17/06. This submission has been reviewed by Dr. Leonard Kapcala, medical officer, Dr. John Duan, Office of Clinical Pharmacology, Dr. Lisa Jones, medical officer, safety team, Dr. Paul Roney, pharmacologist, Dr. Martha Heimann, chemist, and Dr. John Feeney, neurology drugs team leader.

In this memo, I will outline the issues addressed (at/before the meeting, in response to the division's questions asked at the meeting, and in the complete response; these issues constitute, in effect, the sponsor's responses to the issue globally).

Melanoma

Dr. Jones has reviewed these responses in detail in her review of 5/3/06.

Dose Response

The sponsor asserts that it is, in general, difficult to assess dose response, because of the surveillance bias (that is, surveillance was instituted relatively late

in the program) and the potentially long latencies thought to be associated with cancer formation, as well as the fact that patients switched doses throughout TEMPO and PRESTO.

Nonetheless, the sponsor calculated various dose-response data, based on whether or not a tumor was considered to have occurred at the patient's modal dose, highest dose, or the actual dose at the time of tumor diagnosis.

As seen in Dr. Jones's Tables 1, 2, and 3 (pages 9-10), there is no real dose response, and though the point estimates may vary among doses (and placebo; although never monotonically), there is considerable overlap in the 95% CIs.

Cumulative Dose Response

The sponsor has presented an analysis that examines the tumor incidence by cumulative dose. Dr. Jones displays this data (Table 21, page 40). The point estimates, with 95% CIs, are presented below:

Cumulative dose	Cases/1000 Pt-yrs (95% CI)
<295 mg (N=834)	14.3 [6.2, 28.2]
295-932.5 mg (N=626)	1.5 [0, 8.5]
932.5-1917 mg (N=418)	8.0 [2.6, 18.7]
>1917 mg (N=210)	10.5 [3.4, 24.6]

There is no monotonically increasing rate with cumulative dose, although, as Dr. Jones notes, and as was noted in earlier reviews, if one ignores the highest rate in the <295 mg dose stratum (because presumably only pre-existing melanomas were diagnosed in that stratum), then there is a dose response. However, even in that case, there is considerable overlap in the CIs. Also, as noted by Dr. Jones, the sponsor did not explain how these specific cut-offs were obtained.

Immediate vs Delayed Start

Recall that the Agency had been concerned that in TEMPO, there was an apparent increase in tumor incidence in the immediate start group compared to that in the delayed start group, and this increase was related to 6 tumors occurring beyond 24 months in the former group; this was taken as evidence that tumor formation increased with increasing exposure.

The sponsor examined the rates of tumors (per 1,000 patient-years) in various time epochs (0-6 months, 6-12 months, 12-18 months, 18-24 months, and >24 months from the onset of treatment with rasagiline) in the various groups: TEMPO immediate vs delayed; PRESTO immediate vs delayed; total immediate vs total delayed. As can be seen in Dr. Jones's table 4 (page 11 of her review), there is no evidence that, even within a given study (TEMPO or PRESTO), there

is an increase in tumor incidence with increasing duration of exposure (as she notes, the sponsor has slightly updated the number of patients in these time-epoch cells; these new numbers do not materially change the conclusions).

In addition, the sponsor examined the rates of tumor occurrence for the same groups and time epochs, but in this case from the initiation of study drug (rasagiline or placebo). This has the effect of “shifting” the estimates in the previous table referred to (Table 4) for the Delayed start groups to the next (to the right) time epoch column. Dr. Jones displays these findings in her Table 18, page 35-36 of her review). Several findings emerge from these analyses. First, the number of cases is greatest in the >24 month exposure cell for TEMPO immediate and the rate in this cell is greater than the rate in the same cell for TEMPO delayed, but neither is true, as noted earlier, for PRESTO. Also, although the number of cases is greatest in TEMPO Immediate, >24 months, the rate is greatest in TEMPO Immediate, 6-12 months, and the rate for TEMPO Immediate, 0-6 months, is greater than that in TEMPO, Immediate, >24 months. These findings suggest that there may be no meaningful impact of Immediate or Delayed start on the incidence of tumor formation.

The sponsor also addressed the rate of tumor formation by durations beyond those described above; that is, for durations of exposure up to > 5 years. As can be seen in Dr. Jones’s Figure 2 (page 14 of her review), the tumor rates (per 1000 patient years) is as follows:

<1 year (N=834)	11.2
1-3 years (N=578)	4.3
3-5 years (N=356)	10.7
>5 years (N=182)	7.9

One would expect that, if the drug were tumorigenic, tumor rate would increase with increasing exposure, which the data suggests is not so.

However, as Dr. Jones notes, there are considerable dropouts over time; this, of course, has the potential to introduce a bias. With this in mind, the division asked the sponsor to examine the patients who discontinued to see if there risk factors for melanoma were different or similar to those of patients who remained in the study.

Dr. Jones has reviewed the sponsor’s arguments on this point (pages 21-31 of her review). The sponsor specifically looked at age, sex, duration of PD, treatment with l-dopa, and various melanoma risk factors (complexion, hair/eye color, history of childhood severe sunburn, family and personal history of melanoma, inability to tan, freckles, congenital or changing mole, immunosuppression, and presence of large or irregular pigmented lesions) in the continuation and discontinuation cohorts. They examined these risk factors both by specific calendar dates, as well as various epochs of duration of exposure.

As can be seen from Dr. Jones's review, there are some differences in these risk factors between these two groups at some time points, some of which seem relatively consistent within a given factor (see, for example, Dr. Jones's description of the examination of the distribution of men and women in the two cohorts, and the apparent greater proportion of men in the continuation cohort [page 25-6]). Nonetheless, as she concludes, some of these differences would be predicted to be associated with an increased rate of tumor in the continuation cohort, while others would be predicted to be associated with an increased rate of tumor in the discontinuation cohort. The data taken as a whole suggest no important differences (on some, but perhaps not all of the possible, factors that might be important in producing susceptibility to rasagiline-induced tumor formation).

Comparison of melanoma rates between the rasagiline program and the other development programs

As noted earlier, we had concluded that, based on the first 6 tumors noted (prior to systematic surveillance), the tumor incidence in the rasagiline program was higher than that in other development programs (5.8/1000 pt-yrs vs the next highest of 1.6/1000 pt-yrs for pramipexole). The sponsor argues, however, that 3 of the 6 tumors we had included should not be included in this calculus for the following reasons.

On 12/8/00, the sponsor sent a Dear Investigator letter to investigators informing them of the first 4 tumors. A melanoma assessment report (with additional information) was then sent to all investigators on 2/8/01, and the Investigator's Brochure was changed that month as well.

On — two lesions (one diagnosed as melanoma) were removed from patient 064.

On 5/23/00, patient 036 "...reported a lesion on his face and was encouraged to see a dermatologist.", according to Dr. Jones. A biopsy was done on — (almost a year later).

Finally, an advanced melanoma was diagnosed in patient 164, 2 months after initiation of treatment.

The sponsor argues that none of these three cases should be counted in the "unmonitored" rate of tumors for comparative purposes.

Dr. Jones has calculated the rates of tumors (per 1000 pt-yrs) if one, two, or all three of these cases are removed from the calculation (Table 20, page 39 of her review). As she shows, even if all three are removed, the point estimate (2.9/1000 pt-yrs) is still greater than that for the others. However, the 95% CIs

overlap considerably with the rates for the other drugs (even counting all 6 cases, the CIs overlap with those for rotigotine, pramipexole, and tolcapone). Also, as she notes, removing cases for the reasons described is always questionable.

The sponsor also makes an additional argument. The randomization in these studies was 2:1 (drug to placebo). Therefore, the ratio of tumors seen (after the placebo phase) in the drug and (original) placebo groups should be about 2 to 1. In fact, the number of tumors in the drug group was 11, and in the placebo group was 3; the expected numbers would have been 9.3 and 4.7, respectively. According to the sponsor, the actual values did not differ from the predicted ($p=0.26$).

Finally, the sponsor has agreed to perform a randomized study in Phase 4 to further address the question of rasagiline's potential to cause melanoma.

Tyramine sensitivity

The sponsor has agreed to accept language in labeling warning patients to avoid foods/drugs that contain tyramine/amines that could result in serious elevations in blood pressure, and they have committed to perform an adequate tyramine sensitivity study in Phase 4.

Clinical Pharmacology Concerns

We noted in the last AE letter that the sponsor would need to address three important issues:

- 1) They needed to characterize the potential for a kinetic interaction with l-dopa.
- 2) They needed to further characterize if the kinetics of rasagiline were linear down to 1 mg (the recommended dose)
- 3) They needed to address our concerns about the possibility that plasma levels of rasagiline appeared to increase in patients with renal disease, despite the fact that rasagiline is not cleared by the kidney.

Dr. Duan has reviewed the sponsor's responses to these concerns.

Regarding the interaction between rasagiline and l-dopa, the sponsor has provided an analysis of both the PRESTO study (in which all patients were treated with concomitant l-dopa) and the TEMPO study (a monotherapy study, but in which 9% of patients did require treatment with l-dopa).

According to the sponsor, a population PK analysis of the data in the PRESTO study (N=276, with 421 quantifiable rasagiline plasma levels) showed no effect of l-dopa on rasagiline clearance. A population PK study of the 31 patients in the TEMPO study revealed a decrease in rasagiline clearance of about 30%.

However, the sponsor dismisses this latter finding because there were very few samples drawn (2 samples each at weeks 14 and 26, and one sample at week 52; this latter sample was the only one at which patients were receiving concomitant l-dopa). The paucity of sampling makes the results of this analysis unreliable.

In addition, the sponsor demonstrated that the plasma levels obtained for the first several hours after a 1 mg dose in both TEMPO (in which patients did not receive l-dopa) and PRESTO (in which patients received concomitant l-dopa) were essentially identical, suggesting that the addition of l-dopa had no effect on rasagiline clearance (see Dr. Duan's review, page 3).

Dr. Duan does not find the sponsor's arguments about the reliability of the PRESTO population PK analyses compelling, in part because of incomplete information about the details of the timing of plasma level determinations with respect to dosing, and other unknowns. He concludes, however, that there is no a priori reason to expect a kinetic interaction, and, therefore, if the medical team deems the safety experience from the adjunctive studies acceptable, it would be appropriate for the sponsor to perform a definitive interaction study in Phase 4. As we have already concluded that this safety experience is acceptable, I agree that this study can be done in Phase 4.

Dose Proportionality

Previously, the Agency had expressed reservations about the reliability of the sponsor's characterization of the kinetics of a 1 mg dose, the dose to be recommended. These concerns arose out of concerns about the sensitivity of the assay used in those studies that examined the question, the limited number of such studies, and the limited sampling in these studies (many subjects seemed to have levels only at very few time points after dosing, and in some the first level obtained was the highest, suggesting that the plasma-time curve for these patients could not accurately be calculated).

The sponsor re-presented data from several Phase 1 studies that they contend contained adequate sampling data to characterize the kinetics of the 1 mg dose. In particular, they chose to present the data from a theophylline interaction study, in which 18 subjects had plasma levels drawn at 0, 10, 20, 30, 45, 60, 120, 180 minutes and 8, 12, and 24 hours after a 1 mg dose.

Based on these data, the sponsor calculated C_{max}, AUC, and T_{max}. They then compared these values with these same parameters calculated using only plasma level data obtained at the 0, 30, 60, and 240 minute values (from the same study). The AUCs calculated using these different time points were quite similar (8.7 vs 9.5, respectively). The sponsor contends that since there was little difference between the two AUCs, the calculations using the less frequent

samplings validly characterize the kinetics of a 1 mg dose. They therefore conclude that previously calculated kinetic parameters associated with a 1 mg dose, which came from studies that utilized the less frequent sampling scheme, are reliable.

Dr. Duan concludes that, given the established proportionality at doses of 2-10 mg, it would be expected that the levels of drug at 1 mg would be consistent with what would be predicted. Given that these predicted levels were consistent with the levels actually measured at 1 mg, he believes that dose proportionality is no longer an issue. He does discuss potential difficulties with the assay, including difficulties with the assay used for plasma levels in the renal impairment study (see below), but he concludes that the levels assessed (and AUC calculated) from the theophylline interaction study were acceptable because there were more levels measured in this study compared to those in the renal study. Further, the levels determined in the theophylline study were in general greater (for a given dose) than those seen in the renal impairment study. These factors suggest that the levels from the theophylline study were reliable, and more reliable than those from the renal impairment study. For these reasons, he concludes that dose proportionality has been shown at the 1 mg dose.

Renal Impairment

As noted above, we had observed a signal for increased rasagiline plasma levels in patients with mild-moderate renal failure, a finding that was surprising, given the belief that rasagiline is not cleared via the kidney.

To address this concern, the sponsor presented analyses of a study (425) in which patients with mild to moderate renal failure had plasma levels assayed. They conclude that the mean AUC in patients with mild disease had a rasagiline AUC that was 38% higher than normals, and that patients with moderate disease had a rasagiline AUC that was 33% lower than normals.

They also note that there is no detectable rasagiline pre-dose on Day 7 in patients with either mild or moderate disease, but that there are detectable levels of aminoindan (AI), the primary metabolite of rasagiline that is known to be excreted via the kidney. Further, they show that there is no correlation between creatinine clearance and rasagiline levels, but that there is a clear negative correlation between creatinine clearance and AI levels (see Dr. Duan's review, page 7).

Dr. Duan has concluded that, because in this study the assay was problematic, AUCs are unreliable. He therefore examined individual patient levels (see his review, page 8-10). He concludes that there is a "trend" for the levels in the mild patients to be the highest, those in the moderate patients to be the lowest, with the normals in-between, a finding that is difficult, at best, to explain (although it is consistent with the sponsor's findings based on AUC).

Because of the uncertainties described above, Dr. Duan recommends that a definitive renal impairment study be performed in Phase 4. I agree.

Pharmacology

In the 8/4/05 AE letter, we asked the sponsor to repeat an oral embryo-fetal study in the rabbit. Although the letter did not explicitly state that this could be done in Phase 4, Dr. Lois Freed, pharmacology team leader, acknowledges that this was our intent, and the sponsor has agreed to perform this study in Phase 4.

CMC

The 8/4/05 AE included two requests for additional data. Dr. Heimann has concluded that the sponsor's responses to these requests are acceptable.

Other clinical concerns

In the 8/4/05 AE letter, we asked the sponsor to adopt a definition of elevated CPK of 5 times the baseline or greater to qualify an event of rhabdomyolysis for purposes of 15 day AE reporting; they have agreed to do so.

In addition, we noted in the AE letter that although the results of blood pressure monitoring in the clinical trials were reassuring, we wanted the sponsor to perform additional blood pressure monitoring appropriately timed to dose. We noted that this could be done in the tyramine study we expected the sponsor to perform prior to approval.

Of course, as noted above, the sponsor has chosen to accept restrictive product labeling, and therefore will perform the tyramine study in Phase 4. Upon further reflection, given the lack of serious events related to abnormalities in blood pressure, I believe that these additional assessments can still be done in the tyramine study, now to be done in Phase 4.

COMMENTS

The sponsor has presented numerous additional analyses to address our concerns about rasagiline's potential to cause (or induce) melanomas. In particular, they have examined in more detail the relationship between dose and duration of exposure to tumor occurrence. As I have briefly described above, they have noted no important or clear trends for tumor occurrence to be linked either to dose (as assessed both by evaluation of specific and cumulative dose) or duration of exposure (which was examined not only in the comparison between tumor rates in the immediate vs delayed start groups, but for overall

duration of exposure as well). The sponsor's analysis of the effects of (the considerable number of) dropouts on these various estimates, while imperfect, does not raise any obvious signal for a consistent effect on the outcome.

Regarding the comparison of tumor rates among the various drug development programs, the sponsor's attempt to exclude 3 cases in the rasagiline program is somewhat weak, in my view. Although not implausible, I do not believe that we have sufficient information about any of these cases to definitively agree with the sponsor that these cases should be excluded. However, it is true that the 95% CI, even around the estimate derived using all 6 cases, overlaps with those of 3 other programs. Although in my view this is still suggestive, it is only that.

Considering all of the evidence, then, I would conclude that the data presented do not strongly suggest that rasagiline can cause, or induce, melanoma formation. However, given the methodological difficulties inherent in interpreting the data from the studies performed, I cannot conclude with reasonable certainty that rasagiline does not cause, or induce, melanoma formation. For this reason, then, I agree with Dr. Jones that a well designed prospective trial would provide the best opportunity to definitively answer the question. I therefore agree that the sponsor should perform such a study in Phase 4. As described above, they have agreed to do so.

All of the other issues raised in our 8/4/05 AE letter have been addressed sufficiently to support approval at this time, and we have agreed to the language for product labeling with the sponsor. Therefore, we recommend that the attached approval letter, with appended labeling, be issued to the sponsor.

The letter describes the sponsor's agreement to perform the following Phase 4 studies:

- 1) a formal tyramine challenge study
- 2) a dose proportionality study examining doses of 1, 2, and 6 mg
- 3) an evaluation of orthostatic blood pressure and pulse timed to dosing; this will be incorporated into the studies above
- 4) a thorough QT study
- 5) a study in patients with moderate renal impairment
- 6) a large simple trial examining the incidence of melanoma
- 7) an oral embryo-fetal study
- 8) a comprehensive review of the literature to determine the tyramine content of various foods and beverages
- 9) a study evaluating the effects of levodopa/carbidopa on rasagiline kinetics.

Russell Katz, M.D.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Russell Katz
5/16/2006 03:15:34 PM
MEDICAL OFFICER

MEMORANDUM

NDA 21-641 Azilect (Rasagiline Mesylate)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Response to Second Approvable Letter

DATE: May 15, 2006

Background

The reader is referred to my previous reviews about rasagiline, dated June 14, 2004 and July 22, 2005.

On August 4, 2005, the sponsor was sent a second Approvable Letter for rasagiline for the treatment of Parkinson's disease, both as initial monotherapy and as adjunctive therapy with levodopa. The first Approvable Letter was sent on July 2, 2004. In the first Approvable Letter, the review team raised concerns about 1) the occurrence of melanomas in the rasagiline development program and 2) the selectivity of rasagiline for MAO-B and the potential risk of hypertensive reactions with the ingestion of tyramine containing foods (the so-called "cheese reaction"). At the time of the second letter, the review team continued to have the same concerns about tyramine-sensitivity, but the team was somewhat reassured by comparisons of the risk of melanoma in rasagiline development to the risk of melanoma reported in epidemiologic studies of PD patients. Subsequent to the second Approvable Letter, DNP met with the sponsor on December 7, 2005 to specifically discuss remaining questions about the occurrence of melanoma in the rasagiline development program. During the second review cycle, some new questions also arose about the validity of some of the reported pharmacokinetic analyses. The second Approvable Letter noted that clarification of these pharmacokinetic issues would be needed prior to approval.

For this third review cycle, Dr. Lisa Jones of DNP's Safety Group reviewed the sponsor's discussion of the melanoma issue as well as miscellaneous safety issues. Dr. Len Kapcala wrote a clinical review of the tyramine issue, although there were essentially no new data presented by the sponsor. The first Approvable Letter asked the sponsor to conduct an adequate tyramine sensitivity study, incorporating a number of important elements that were outlined in the letter, or offered the sponsor the option of Approved Labeling restricting use to patients on tyramine-restricted diets. The sponsor has chosen the latter option and has agreed to conduct the tyramine study post-approval.

Dr. John Duan has reviewed the miscellaneous pharmacokinetic issues that remained.

The review team are all recommending an Approval Action at this time.

The sponsor's initial response to the second Approvable Letter was dated January 20, 2006. That was not considered a complete response by DNP because the sponsor did not address the miscellaneous pharmacokinetic issues from the second Approvable Letter. (Instead, in the January 20 submission, the sponsor made commitments to perform studies post-approval to address the PK issues.) The sponsor met with DNP on March 3, 2006 to discuss the agency's PK questions. A subsequent March 17 submission was considered a complete response to the second Approvable Letter.

Efficacy

The sponsor has clearly established the efficacy of rasagiline both as monotherapy and as an adjunct to levodopa in more advanced patients. Previous reviews have discussed the single randomized placebo-controlled trial in early PD (TEMPO) and the 2 adjunctive trials in more advanced PD (PRESTO and LARGO).

In monotherapy, the recommended dose will be 1 mg administered once daily. In the TEMPO study, the 1 mg arm outperformed the 2 mg arm.

As adjunctive therapy, the recommended initial dose will be 0.5 mg administered once daily. For insufficient clinical response, the dose may be increased to 1 mg once daily.

Melanoma

During the first review cycle, Dr. Lisa Jones performed an age- and sex-matched comparison of the melanoma risk in the rasagiline program to the melanoma risk in a North American study of the general adult population that included active surveillance for melanoma (the AAD or American Academy of Dermatology study). This resulted in an Observed/Expected Ratio of 4.7 (95% CI: 2.3-8.7). In my review at the time, I wrote, "It seems unlikely that such an increase in risk could be explained by the presence of Parkinson's disease alone."

During the second review cycle, Dr. Lisa Jones performed a similar comparison between EP002, a North American study that included PD patients (treated with currently-available medications and not rasagiline) and incorporated active surveillance for melanoma, and the AAD study. That comparison suggested a 5-fold increase in melanomas in PD patients compared to the general background population. Thus, the presence of PD alone could explain a high risk of melanoma.

Although, Dr. Jones did not formally compare the EP002 results to the rasagiline database, the risk of melanoma was obviously similar between these 2 groups.

A Danish study published in 2005 reported that, in the absence of active surveillance, the risk of melanoma in PD patients was 2-fold greater than in the background population.

Together, this epidemiologic data provides reassurance that the risk seen in the rasagiline database can be explained by a higher risk in PD patients in general.

The last Approvable Letter did note that there were some observations that were still troubling.

First, the rate of melanoma in the rasagiline database (including only tumors detected before the institution of active surveillance) was 5.8 tumors/1000 pt-years of exposure, a rate that was higher than that seen for other PD treatments for which we have data. The sponsor has responded to this by arguing that, of the 6 melanomas that contributed to this computed rate, only 3 should really be counted. Two of the 6 were diagnosed after investigators had already been alerted in some form to the occurrence of melanomas with rasagiline. Thus, even though active surveillance had not formally begun, the investigators would have been expected to have heightened vigilance for the problem. A third melanoma was invasive and was diagnosed very soon after rasagiline was started and would be considered very unlikely to be due to the drug. Including only the remaining 3 melanomas, the risk would be about 3/1000 pt-years. This is comparable to the other rates for other drugs for which we have data. In my 2004 rasagiline review, I discuss a comparator group taken from 3 PD studies conducted by the Parkinson's Study Group (PSG), an independent group of PD investigators. Across the 3 studies, there were 1296 patient-years of exposure among PD patients and 3 cases of melanoma were recognized. The incidence density for rasagiline (using only the 3 cases discussed in this paragraph), 3 per 1000 PYs, is comparable to the PSG incidence density, 2.3 per 1000 PYs.

Second, comparing tumor incidence between the immediate and delayed start phases of the TEMPO study revealed an increased incidence in the immediate-start group, accounted for mainly by 6 tumors diagnosed after 24 months of exposure. This late finding that distinguished the 2 groups was not mirrored in the PRESTO study. In my review, I noted that, in PRESTO, there was still a greater risk of melanoma in the immediate-start group. Even though the pattern in PRESTO showed an early peak versus a late peak, I questioned whether the overall excess across both studies for the immediate-start groups was not concerning by itself. After much discussion and on reconsideration, I now believe the failure to see the same pattern in both studies diminishes the value of the delayed-start analyses for our overall conclusions.

Dr. Jones also notes that, while the number of cases was highest in the >24 months stratum for the TEMPO immediate-start group, the highest rates (when adjusted for exposure) for that same immediate-start group actually occur in the 6-12 month stratum. This would also seem to suggest that there is no real pattern to the data in the immediate- vs delayed-start analyses.

To further clarify the issue, the sponsor has agreed to conduct a large simple trial post-approval to compare melanoma rates between patients exposed and unexposed to rasagiline. I previously believed such a study should be done pre-approval, but I have reconsidered that position and now believe that it seems unlikely that rasagiline alone is

associated with an increase in the risk of melanoma. It is therefore acceptable to perform the study post-approval.

Dr.Jones has also reviewed a new dose-response analysis performed by the sponsor which uses cumulative dose as the exposure variable. In that analysis, there is no clear dose-response relationship.

A previously reviewed analysis, the incidence of melanoma by duration of rasagiline treatment, had not shown a monotonic increase in incidence with increasing duration of exposure. Dr.Jones had asked the sponsor to look at melanoma risk-factor data on the dropout cohorts. Dr.Jones has reviewed that data and concluded that there are no apparent differences in melanoma risk factors in the dropout cohorts. Therefore, the lack of an increasing incidence with increasing exposure appears to be a valid result.

Preclinical Data

At the time that I wrote my 2005 rasagiline review, the review team was aware that a single melanoma had occurred in a high-dose animal in a 2-year rat carcinogenicity study. Because it was thought to be an extremely rare tumor in that setting, the finding added to the review team's overall concern about melanoma. Subsequently, Dr.Loïs Freed reviewed the significance of this finding in her supervisory memo dated August 3, 2005. Dr.Freed wrote, "Although rare (<1%), melanomas do occur spontaneously in albino animals." In light of that, a single melanoma could represent a background event.

Additional Safety Issues

Dr.Jones also has addressed the sponsor's proposal for a formal QT study post-approval and the sponsor's criterion for submitting, as 15-day reports, potential cases of rhabdomyolysis. Dr.Jones is in agreement with the sponsor's approach on both of these issues.

Clinical Pharmacology Issues

Dr.John Duan has reviewed the remaining clinical pharmacology issues. These were the main topics of a meeting between the sponsor and DNP on March 3, 2006. Having reviewed these issues, the Clinical Pharmacology team believes that rasagiline can be approved at this time, with several commitments to conduct post-approval studies.

1. The sponsor was asked to formally evaluate the effect of levodopa on rasagiline clearance. There are data from 2 different population PK analyses that provide conflicting results. Both the sponsor and Dr.Duan agree that a dedicated interaction study is needed. However, given the safety experience with the combination of rasagiline and levodopa in the Presto study, the review team has agreed that the study can be done as a Phase 4 commitment.

2. The sponsor was asked to conduct a renal-impairment study in patients with moderate to severe renal impairment. Previous results were believed to be unreliable. Dr.Duan has plotted available results and believes the data support no effect of moderate renal impairment. Pending results from a Phase 4 study, labeling will indicate that no dose adjustment is needed in patients with mild renal impairment.

3. The sponsor was asked to conduct a dose-proportionality study because the PK at a dose of 1 mg/day was believed to be unreliable. Dr.Duan argues that, given the linearity shown from 2mg to 10mg, it would extremely unusual to have non-linearity below 2mg. The sponsor is currently conducting a study to investigate this further; Dr.Duan believes there is enough evidence presented now to support approval with submission of the new results as a Phase 4 commitment.

Also, of note, the sponsor will collect additional data on orthostatic blood pressure and pulse measurements timed to dosing as part of some of these studies.

Recommendations

1. The sponsor should be sent an Approval Letter with labeling.
2. The sponsor has agreed to a number of post-approval commitments which should be detailed in the Approval Letter.
2. The sponsor has committed to work with physician societies to agree on appropriate dermatologic monitoring in patients with PD. As part of that process, it would be helpful if the details of the AAD-EP002 analysis were published.

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

/s/

John Feeney
6/1/2006 02:38:30 PM
MEDICAL OFFICER

**Clinical Review of Sponsor's Complete Response to
Approvable Letter for Tyramine Sensitivity and Related
Pharmacokinetic Issues, and Label for Tyramine Sensitivity,
Efficacy, and Dosing**

Application Type	NDA
Submission Number	21641
Submission Code	AZ
Letter Date	3/17/06
Stamp Date	3/17/06
PDUFA Goal Date	5/17/06
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	5/12/06
Established Name	rasagiline
(Proposed) Trade Name	Azilect
Therapeutic Class	MAO-B inhibitor
Applicant	TEVA Neurosciences
Priority Designation	S
Formulation	tablet
Dosing Regimen	once daily
Indication	Monotherapy of Early Parkinson's Disease and Adjunctive Therapy of Advanced Parkinson's Disease
Intended Population	Early and Advanced Parkinson's Disease

Table of Contents

1	INTRODUCTION AND BACKGROUND.....	3
1.1	REGULATORY HISTORY.....	3
1.2	ABSTRACT OF EXECUTIVE SUMMARY OF REVIEWER’S LAST REVIEW INCLUDING OVERALL PERSPECTIVE / ASSESSMENT, CONCLUSIONS, AND RECOMMENDATIONS FROM THE LAST REVIEW OF THE SPONSOR’S COMPLETE RESPONSE TO THE APPROVABLE LETTER.....	4
1.3	DNP APPROVABLE LETTER (8/4/05) RECOMMENDATIONS REGARDING TYRAMINE SENSITIVITY AND RELATED PHARMACOKINETIC ISSUES.....	6
2	SPONSOR’S RESPONSE (3/17/06) TO APPROVABLE LETTER (8/4/05).....	9
3	CLINICAL PHARMACOLOGY REVIEWER (DR. JOHN DUAN) COMMENTS OF SPONSOR’S COMPLETE RESPONSE	11
4	CLINICAL LABELING REVIEW	12
4.1	CLINICAL REVIEWER’S TRACKED CHANGES REVISIONS OF THE LABEL RELATIVE TO THE ORIGINAL FDA PROPOSED LABEL IN THE ORIGINAL APPROVABLE LETTER	12
1.1	SPONSOR’S TRACKED CHANGES REVISIONS OF THE LABEL RELATIVE TO THE ORIGINAL FDA PROPOSED LABEL IN THE ORIGINAL APPROVABLE LETTER	27

Appears This Way
On Original

1 INTRODUCTION AND BACKGROUND

1.1 Regulatory History

The IND for this NDA was filed on 8/5/94. The sponsor submitted NDA 21641 on 9/5/03. On 7/2/04, the Agency issued an approvable letter describing several concerns. The most significant concerns revolved around the Agency's concern: 1) that the risk of increased tyramine sensitivity (i.e. the selectivity of MAO inhibition for MAO-B vs MAO-A) to rasagiline had not been adequately characterized at various doses, including 1 mg and 2 mg daily; and 2) for the risk of developing melanoma or acceleration of growth of melanoma that was already present. The Agency had recommended that the sponsor conduct a new study to characterize the risk of increased sensitivity to tyramine. The Approvable letter further noted that if the sponsor did not want to conduct the recommended tyramine study, then the product labeling would need to require that patients restrict the diet with regard to tyramine containing products.

The sponsor (including its consultants Dr. — and Ira Shoulson) met with the DNDP on 9/27/04 to discuss the Agency's concerns about increased sensitivity to tyramine and melanoma. The sponsor argued that it did not think that there were concerns for a risk of tyramine hypertensive reaction at 1 mg daily rasagiline. The DNDP informed the sponsor that it was welcome to make whatever arguments it wanted to convince the Agency that another tyramine study was not necessary prior to approval nor that dietary tyramine restriction was needed in the absence of the sponsor conducting the recommended tyramine study prior to approval. In that meeting this reviewer specifically "noted that, in his personal view, the sponsor's data and package containing the sponsor's various arguments against safety concerns for tyramine reactions (with rasagiline treatment) did not suggest anything new that changed his view about the need for the tyramine challenge study recommended by the DNDP."

On 11/4/04 the sponsor submitted an electronic Response to the Approvable letter. On 8/4/05, the Agency issued another approvable letter with persisting, unresolved concerns related to the risk of melanoma, and tyramine sensitivity, and concerns also related to pharmacokinetic (PK) issues (dose proportionality, effect of age and gender on rasagiline, potential for levodopa interaction with rasagiline PK, and need for repeat comprehensive study of renal impairment. This review will review the sponsor's response solely on the concern about increased sensitivity.

On 1/20/06, the sponsor submitted another electronic Response to the Approvable letter. The DNP did not file this response because it was judged to be incomplete because the sponsor did not explicitly, adequately address the DNP concerns about the PK issues. The sponsor had planned to address these issues in phase 4, post-approval despite the fact that the Agency did not offer the possibility of conducting PK studies in phase 4.

On 3/3/06, the DNP met with the sponsor to discuss the resubmission of the Response to the Approvable letter. This revised response was submitted on 3/17/06.

1.2 Abstract of Executive Summary of Reviewer's Last Review Including Overall Perspective / Assessment, Conclusions, and Recommendations from the Last Review of the Sponsor's Complete Response to the Approvable Letter

Reviewer's Overall Perspective / Assessment

- **Overall, the sponsor's response on the tyramine sensitivity issue is mainly a recapitulation of previous arguments articulated in the original submission. This response did not include any new substantive data nor new analyses that had not been available previously. In many instances, the sponsor has reviewed data or publications in a somewhat superficial manner and did not seem to provide a very critical, objective assessment of data and issues of concern. It is the sponsor's responsibility to show that rasagiline is safe and especially with respect to risk of tyramine sensitivity and hypertensive "cheese" reactions. When the assessment of the safety of rasagiline related to tyramine sensitivity is largely indeterminate because of limitations in the extent and quality of data collected, the burden should not rest with the Agency to guess and hope that rasagiline is safe relative to tyramine sensitivity. It is not appropriate nor prudent for the Agency to approve the drug and let the tyramine sensitivity issue be resolved post-approval as a result of the post-marketing safety experience. My overall assessment is that the sponsor has not adequately demonstrated the safety of rasagiline relative to tyramine sensitivity and needs to do this prior to approval.**

Reviewer Conclusions :

- 1. The available data have not adequately characterized the effect of rasagiline on tyramine sensitivity and thus the risk for serious hypertensive "cheese reactions" cannot be adequately assessed relative to when tyramine restriction is necessary and when tyramine restriction is unnecessary.**
- 2. There are 3 other significant considerations (1. rasagiline does not represent major advance as medical option for Parkinson's Disease; 2. unresolved, serious concern about risk of melanoma with rasagiline; 3. serious risk that a higher rasagiline 2 mg daily dose will be used because of a publication suggesting possible delay of Parkinson's Disease and this dose is associated with increased risk for hypertensive tyramine-related "cheese" reaction) that support my recommendation for an approvable action at this time. I view these considerations as supportive of my recommendation and would still recommend the same approvable action at this time even if these 3 considerations did not exist.**
- 3. The sponsor must conduct the tyramine challenge study (under fasting conditions) previously recommended by the Agency prior to approval and adequately characterize the risk for increased tyramine sensitivity.**

Recommended Action :

I recommend an approvable action at this time relative to the need to collect additional data to characterize the risk of tyramine sensitivity to rasagiline treatment.

Recommendations

Requirements Prior to Approval

1. Conduct a randomized, double-blinded, placebo-controlled study (under fasting conditions) to characterize the risk more precisely and comprehensively for rasagiline-induced tyramine sensitivity. Such a study should be designed to address concerns, problems, limitations and shortcomings of Study P94159. Such considerations include :
 - 1) studying larger numbers of older (30 – 60 years old), healthy subjects ($N \geq 20$ per treatment group) including males and females
 - 2) comparing multiple treatment groups including 1, 2, 4, 6 mg rasagiline daily, placebo, selegiline 10 mg daily mg BID), and positive control group (non-selective MAO inhibitor)
 - 3) requiring 3 consecutive systolic blood pressure increments ≥ 30 mm Hg to define tyramine threshold dose relative to mean of 3 pre-tyramine systolic blood pressures after blood pressure monitoring at 5 minute intervals over 3 hours
 - 4) administering multiple tyramine challenge doses for pre-treatment (50, 100, 200, 300, 400, 500, 600, 700, 800 mg) and post-treatment (12.5, 25, 50, 100, 200, 300, 400, 500, 600, 700, 800 mg) administered on separate consecutive days
 - 5) ensuring that the tyramine used for challenges has adequate biological potency
2. Conduct a dose proportionality PK after multidosing (e.g. 0.5, 1, 2, 4, 10 mg) of rasagiline at steady state. This study could also be designed to answer age and gender questions by nesting appropriate stratification of subjects by age (elderly ≥ 65 years old vs younger/non-elderly < 40 years old) and gender.
3. Conduct a renal impairment PK study after multidosing (1 mg) of rasagiline because results of the previously conducted renal studies are not deemed reliable and these are important factors that could increase rasagiline exposure.

Other Recommendations (Not Required for Approval)

1. Conduct a formal PK study comparing the PK parameters of 1 mg rasagiline daily treatment (steady state) with respect to age (elderly \geq 65 years old vs younger $<$ 40 years old) and gender.
2. Conduct a formal PK study assessing the effect of LD on rasagiline PK parameters / exposure.

1.3 DNP Approvable Letter (8/4/05) Recommendations Regarding Tyramine Sensitivity and Related Pharmacokinetic Issues

Tyramine

We continue to believe that you have not provided adequate evidence that a 1 mg dose of rasagiline, taken with a high tyramine content meal, cannot produce hypertensive reactions. Although we recognize that there is no signal for such a risk in the NDA database, we believe that the data you have provided to address this question are inadequate.

As you know, we have serious concerns that the tyramine product you used in all of your challenge studies did not exhibit an appropriate degree of potency/bioavailability. This (among other considerations) calls into question the results of all of these challenge studies. In particular, as we noted in our previous letter, many patients in the Paris study required 800 mg of tyramine for a

**APPEARS THIS WAY
ON ORIGINAL**

threshold response or did not exhibit a blood pressure response to a tyramine dose of 800 mg, an observation in tyramine challenge studies that is unique in our experience. In response, you assert that the literature suggests that a significant proportion of unselected subjects do not respond to such a dose of tyramine (this assertion is primarily based on the description of several challenge studies that excluded subjects who did not respond to doses of tyramine up to 600 mg). You have not, however, presented empirical data showing that any patient has actually ever been excluded from any challenge study because they did not respond to a tyramine dose of 800 mg. For this major reason (and previously expressed concerns that this study enrolled very few patients who showed threshold responses and no elderly subjects), we continue to conclude that the results of the Paris study cannot be considered reliable.

In addition to this concern, there is reason to believe that in your three other tyramine challenge studies, the timing of the post-meal blood pressure monitoring was such that any significant blood pressure elevations might have been missed. Specifically, as we had previously noted, the literature suggests that the maximum increase in blood pressure seen after a meal to which tyramine is added (as was done in your studies) typically occurs at least 2 ½ hours after the meal, times in which the blood pressure monitoring in your studies was relatively sparse. You have presented no clear evidence that this is not the case.

Furthermore, the published literature clearly shows that tyramine doses required to achieve a threshold pressor response increase several fold when tyramine is added to a meal compared to administration under fasting conditions. Thus, one would not expect tyramine threshold responses to the relatively low doses of tyramine used (i.e. 25-75 mg) given with food unless the tyramine sensitivity was markedly increased. In particular, one publication on subjects with increased tyramine sensitivity (increased 5 fold by drug treatment) showed that when tyramine was added to a meal, subjects required 150 mg – 500 mg tyramine to achieve a threshold pressor response despite the fact that a drug had increased fasting tyramine sensitivity several fold. Thus, we have no assurance that the absence of pressor responses in your studies in which tyramine was added to food or administered near a meal represents true negative responses.

In addition, the home blood pressure monitoring in the PRESTO study suffered not only from the deficiency cited above, but also from the fact that the tyramine content of the meals was unknown (not being a challenge study, this would be important information to have in order to interpret the results).

We recognize that you assert that the typical tyramine-rich meal contains far less tyramine than is typically used in formal tyramine challenge studies. This is undoubtedly true, but, for the reasons cited above, we do not believe that you have adequately addressed the effects of rasagiline when given with such a tyramine-rich meal.

Finally, as you know, we believe the data do suggest that there may be an increase in tyramine sensitivity at the 2 mg dose. There is also evidence that some patients who receive a 1 mg dose may achieve plasma levels close to those seen in the typical patient receiving 2 mg (e.g., patients on CYP 1A2 inhibitors, potential non-linearity). This further increases our concerns.

For these reasons, we continue to believe that you must address the question of rasagiline's potential to cause hypertensive reactions in the absence of dietary restrictions prior to approval. As we have said previously, this may be done in Phase 4 if you are willing to adopt labeling requiring dietary tyramine restrictions at recommended doses. A formal fasting tyramine challenge test is the standard way to

evaluate this potential effect. Therefore, we re-iterate our original request to perform a formal tyramine challenge study including the following elements:

- 1) Use of an appropriate number (e.g. ~ 20) of patients (e.g. equal number of older males and females: 40-70 years) receiving rasagiline as monotherapy.
- 2) Use of an appropriate positive control treatment group, if possible
- 3) Use of an adequately potent tyramine product demonstrated to be bioavailable. (tyramine should be administered in the fasting state)
- 4) Use of multiple dose levels (e.g. 0.5, 1, 2, 3, 4 mg) of rasagiline, including doses that produce exposures approximately equal to the maximal exposures expected in patients receiving therapeutic doses of rasagiline (e.g. maximally metabolically inhibited, patients with mild hepatic insufficiency, or patients with multiple, factors separately resulting in an additive risk of significantly increased exposure, etc.).
- 5) Use of selegiline (5 mg BID) as an additional treatment group for comparison to rasagiline
- 6) Use of baseline/pre-treatment tyramine doses of 25 mg, 50 mg, and 100 mg and dose increments above 100 mg of 100 mg up to 800 mg. Post-treatment tyramine should start at 12.5 mg because subjects could be very sensitive to 25 mg and use otherwise similar dosing as baseline/pre-treatment. Tyramine doses should be administered on separate days.
- 7) Use of a blood pressure criterion of three consecutive systolic increases of at least 30 mm Hg with close monitoring at 5 minute intervals over at least 2 hours and collection of at least 3 blood pressure measurements within 15-30 minutes prior to tyramine administration to serve as an integrated average blood pressure for comparison to a threshold pressor response after tyramine
- 8) Measurement of plasma tyramine at 30 minutes after each tyramine challenge (≥ 25 mg) in all treatment groups pre- and post-treatment
- 9) It is possible that a more ecologically valid test might be acceptable to address your contention that the large doses given in the typical challenge study are clinically irrelevant.

Clinical Pharmacology and Biopharmaceutics

- 2) Although you have agreed to accept our proposed labeling language regarding the discrepant results for the effect of levodopa on rasagiline clearance, we had asked you to formally evaluate this effect. We continue to believe that an adequate characterization of this effect is necessary.
- 3) We do not believe that you have adequately characterized the dose proportionality of rasagiline. Therefore, we ask you to perform a formal dose proportionality study. This study should enroll at

least 8 subjects (4 males, 4 females) in each age group (40-60; >65 years old) at each dose tested (the study should evaluate at least the following doses: 1 mg, 2 mg, and 6 mg).

- 4) We note a doubling of the plasma levels of rasagiline in patients with mild renal dysfunction compared to normals. Because this finding was unexpected, we believe that patients with moderate to severe renal dysfunction should be formally evaluated (we recognize that you have done so, but we believe the data in these latter patients is unreliable because only a very few patients had adequate plasma sampling).

2 SPONSOR'S RESPONSE (3/17/06) TO APPROVABLE LETTER (8/4/05)

Reviewer's Overview of Sponsor's Complete Response to Approvable Letter

The sponsor's response contains a limited number of issues (tyramine sensitivity and pharmacokinetic (PK) factors that can increase rasagiline exposure and thereby tyramine sensitivity) with which I have been involved. Previously, my reviews focused on efficacy and tyramine sensitivity of rasagiline along with pharmacokinetic (PK) issues that could increase exposure and thereby, sensitivity to tyramine. There were no outstanding issues or concerns with the efficacy of rasagiline. There were concerns that the sponsor had not adequately characterized the dose-response relationships of rasagiline with tyramine sensitivity. The sponsor opted at this time to seek approval of rasagiline with dietary tyramine restrictions (one of the options allowed by DNP) rather than conduct a tyramine sensitivity study prior to approval. Thus, my comments here are focused on the sponsor's phase 4 commitment to conduct an adequate study characterizing the tyramine sensitivity to rasagiline and the sponsor's position about conducting a phase 4 PK studies characterizing factors (concomitant levodopa use, age, gender, renal impairment). My review will also briefly on some of the PK issues with which I have been involved previously along with the Clinical Pharmacology reviewer because of the their potential importance and relevance to increased rasagiline exposure and increased sensitivity to tyramine. I have discussed these issues with the Clinical Pharmacology reviewer, Dr. John Duan. However, a detailed review of these issues has been conducted by Dr. Duan and the reader should refer to his review.

*Appears This Way
On Original*

Teva's Post-approval (Phase 4) Commitments With Which This Reviewer Has Been Involved are provided below :

1. A formal tyramine challenge study in the fasted state. This trial will incorporate the following elements:
 - An appropriate number of subjects (e.g. approximately 20 per arm, equal number of males and females 40 to 70 years of age)
 - An appropriate positive control
 - The use of multiple dose levels of rasagiline
 - The use of selegiline as an additional comparator
 - The use of baseline/pre-treatment tyramine doses of 25, 50, and 100 mg and dose increments above 100 mg of 100 mg up to 800 mg. Post-treatment

tyramine will use a similar dosing as pre-treatment, but starting doses will be lower. Tyramine doses will be administered on separate days

- The use of blood pressure criterion of three consecutive systolic increases of at least 30 mm Hg with close monitoring at 5 minute intervals over at least 2 hours and collection of at least 3 blood pressure measurements within 15-30 minutes prior to tyramine administration to serve as an integrated average blood pressure for comparison to a threshold pressor response after tyramine
- Measurement of plasma tyramine at 30 minutes after each tyramine challenge study in all treatment groups.

Protocol submission Date: July 30, 2006¹

Study Start Date: December 30, 2006

Final Report Submission Date: December 30, 2008

¹ The protocol submission date will be approximately 60 days after an approval action; the date provided is based on 2 month review with an action taken in late May 2006.

Clinical Reviewer Comment :

- The sponsor has committed to conducting a phase 4 tyramine sensitivity study that incorporates important, desired elements recommended by the DNP. This commitment appears adequate at this time. Review of a full study protocol will be necessary prior to conducting the study and determining the adequacy at that time.

Appears This Way
On Original

4. To investigate the dose-proportionality of daily doses of rasagiline (1, 2 and 6 mg) following multiple-dose administration in healthy young and elderly subjects and the effect of levodopa/carbidopa (single dose) on the pharmacokinetics of rasagiline (multiple dose). A secondary objective of this study will be to evaluate orthostatic blood pressure and pulse rate timed to rasagiline dosing.

Protocol submission Date: January 20, 2006
Study Start Date: March 30, 2006
Final Report Submission Date: February 28, 2007

5. To compare the plasma pharmacokinetic parameters of rasagiline and 1-aminoindan (1-AI) following once daily repeated dosing of a 1 mg tablet of rasagiline for 8 days in healthy subjects and in subjects with moderate renal impairment.

Protocol submission Date: January 20, 2006
Study Start Date: March 30, 2006

Clinical Reviewer Comment :

- See my comments in the following section regarding the Clinical Pharmacology reviewer's comments of the Sponsor's Complete Response.

3 CLINICAL PHARMACOLOGY REVIEWER (DR. JOHN DUAN) COMMENTS OF SPONSOR'S COMPLETE RESPONSE

The following summary comments were abstracted from the Clinical Pharmacology reviewer's review. For additional details and detailed arguments, the reader should refer to the Clinical Pharmacology review.

COMMENTS

1. The available data show inconclusive and conflicting results regarding the drug interaction between levodopa and rasagiline. To elucidate this drug interaction and provide clear instruction for the combination use, a drug interaction study between levodopa and rasagiline is recommended for Phase IV commitment. In the study, both the effect of rasagiline on levodopa and the effect of levodopa on rasagiline should be examined. As planned by the applicant, this study should involve young and elderly subjects to detect the age effect. In addition, the gender effect should be examined in this study by enrolling adequate number of males and females.
2. The renal impairment study results were not meaningful to allow a clear instruction for dosing in renal impairment patients. As a Phase IV commitment, the planned renal impairment study should first investigate the differences between the assay method used in study 430 (— SOP 659 Version D) and that used in study 425 (— SOP

659 Version B). If Version D used in study 430 is a more sensitive method, it should be used in the study to be conducted.

3. No additional dose proportionality study is necessary.

Clinical Reviewer Comments :

- **I agree with the Clinical Pharmacology reviewer (Dr. Duan) that a drug-drug interaction (DDI) study should be conducted in phase 4 to characterize if there is (and the extent if so) a DDI between rasagiline and levodopa (LD).** This is a potentially important issue to resolve because once an adequate study has been conducted to characterize tyramine sensitivity with rasagiline, it may not be necessary for all patients to restrict dietary tyramine. Dietary tyramine restriction (and restriction of amines in medications) may only be necessary in patients who have one of more factors that increase PK exposure of rasagiline to a sufficient level there is a significant risk of hypertensive crisis/"cheese" reaction. Characterizing the magnitude of an increase in rasagiline exposure related to concomitant LD treatment will allow one to assess how this factor along with others may increase the sensitivity to tyramine and indicate whether restriction should be conducted for dietary tyramine and amines in medications once the dose-response relationships of rasagiline for tyramine sensitivity have been characterized.

Along this same line of thinking, the sponsor should conduct an adequate phase 4 study to characterize if there is a PK effect of age (e.g. "elderly" = ≥ 65 years vs "young" patients such as 35-55 years) and/or gender. Effects of age and/or gender that increase rasagiline PK exposure can be considered in determining whether restriction of dietary tyramine and amines in medications is necessary after dose-response relationships of rasagiline for tyramine sensitivity have been characterized. **All of this information (i.e. effects of LD, age , gender) could potentially be obtained in a single PK study.**

- **I agree with the Clinical Pharmacology reviewer (Dr. Duan) that a renal impairment study should be conducted in phase 4.**
- **I agree that it is not necessary to conduct a dose proportionality PK study.**

4 CLINICAL LABELING REVIEW

4.1 Clinical Reviewer's Tracked Changes Revisions of the Label Relative to the Original FDA Proposed Label in the Original Approvable Letter

Relevant sections of the label dealing with rasagiline-related tyramine sensitivity, efficacy, and dosing are shown.

73 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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

/s/

Leonard Kapcala
5/15/2006 04:15:04 PM
MEDICAL OFFICER

John, Here is my review that you've seen with
the exception that the Clin Pharm final comments
have been added to replace the draft comments.
Please sign and let me know if any
questions. Thanx. Len

John Feeney
6/10/2006 06:39:03 PM
MEDICAL OFFICER

**CLINICAL SAFETY REVIEW:
TEVA'S RESPONSE TO THE SECOND APPROVABLE
LETTER FOR RASAGILINE**

Application Type NDA
Submission Number 21-641
Submission Code AZ

Letter Date January 20, 2006
Stamp Date January 20, 2006
PDUFA Goal Date May 17, 2006

Reviewer Name M. Lisa Jones, MD, MPH
Review Completion Date May 1, 2006

Established Name Rasagiline
(Proposed) Trade Name Azilect®
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

TABLE OF CONTENTS

1. INTRODUCTION AND BACKGROUND	4
1.1 DATA SOURCES	4
1.1.1 Sponsor Documents	4
1.1.2 FDA Documents	4
1.2 REVIEW CONTENT	5
2. DECEMBER 7TH MEETING BRIEFING PACKET	5
2.1 SPONSOR INTRODUCTION	5
2.2 BACKGROUND	8
2.3 DOSE-RESPONSE ANALYSIS	8
2.4 IMMEDIATE VS. DELAYED START ANALYSIS	10
2.5 ADDITIONAL SPONSOR POINTS	12
2.5.1 Increased Rates of Melanoma in the Rasagiline Development Program Compared to Other PD Development Programs	12
2.5.2 Melanoma Rate in the Rasagiline North American Clinical Program and Comparison to Control	13
2.5.3 Melanoma Incidence Rate by Duration of Exposure	13
2.5.4 Comparison of EP002 to the Rasagiline Development Program	14
2.5.5 Detection Bias: Non-Melanoma Skin Cancers	15
2.5.6 Non-Clinical	15
2.6 SPONSOR-PROPOSED MELANOMA RISK MANAGEMENT PROGRAM	17
2.6.1 Enhanced Safety Monitoring	18
2.6.2 Risk Minimization Program	18
2.6.3 Labeling	18
2.6.4 Public Education Campaign	19
2.7 LARGE SIMPLE RANDOMIZED CONTROLLED TRIAL (PHASE IV)	19
2.8 SPONSOR SUMMARY AND CONCLUSIONS	20
3. SPONSOR RESPONSE TO POST-MEETING FDA QUESTIONS	21
3.1 MELANOMA RISK FACTOR COMPARISON IN CONTINUING AND DISCONTINUING SUBJECTS	21
3.1.1 FDA Question to Teva	21
3.1.2 Sponsor Response with Reviewer Comments	22
3.2 IMMEDIATE/DELAYED EXPOSURE: UPDATED DATA	31
3.2.1 FDA Question to Teva	31
3.2.2 Sponsor Response with Reviewer Comments	32
3.3 PRE-SCREENING MELANOMA CASES	36
3.3.1 FDA Question to Teva	36
3.3.2 Sponsor Response with Reviewer Comments	37
3.4 DOSE-RESPONSE: CUMULATIVE DOSE	40
3.4.1 FDA Question to Teva	40
3.4.2 Sponsor Response with Reviewer Comments	40
3.5 DISCONTINUATION DUE TO PATIENT/PHYSICIAN DECISION	41
3.5.1 FDA Question	41
3.5.2 Sponsor Response with Reviewer Comments	41
4. PHASE IV STUDY PROTOCOL	45
4.1 OVERVIEW	45
4.2 SUBJECTS	46
4.3 STUDY VISITS	47

4.4 MELANOMA SCREENING AND DIAGNOSIS.....	47
4.5 SAMPLE SIZE	47
4.6 TREATMENT PROTOCOL.....	47
4.7 STATISTICAL METHODS.....	48
5. SAFETY UPDATE.....	48
5.1 ADVERSE EVENTS.....	48
5.1.1 <i>Exposure and Overview</i>	48
5.1.2 <i>Changes from Previous Safety Summary</i>	48
5.1.3 <i>Common AEs</i>	49
5.1.4 <i>Cardiovascular Events</i>	50
5.1.5 <i>Neuropsychiatric Adverse Events</i>	50
5.2 DEATHS	51
5.3 SERIOUS ADVERSE EVENTS (SAEs)	54
5.3.1 <i>Changes from Previous Safety Report</i>	54
5.3.2 <i>SAEs in the Pharmacovigilance Database</i>	55
5.4 DISCONTINUATIONS.....	57
5.4.1 <i>Discontinuations due to Physician/Patient Decision</i>	57
5.4.2 <i>Discontinuations due to Adverse Event</i>	58
5.4.3 <i>Summary of New Discontinuations</i>	58
5.4.4 <i>Expedited SAE Report: Thrombocytopenia</i>	60
5.4.5 <i>Other Events of Clinical Importance</i>	61
6. OTHER REMAINING SAFETY ISSUES	61
6.1 RHABDOMYOLYSIS	61
6.1.1 <i>FDA Comment</i>	61
6.1.2 <i>Sponsor Response</i>	62
6.2 THOROUGH QT STUDY	62
7. DISCUSSION AND CONCLUSIONS.....	63
7.1 OVERALL MELANOMA CONCLUSION	63
8. ATTACHMENTS.....	66
8.1 MINUTES FROM DECEMBER 7, 2005 MELANOMA MEETING WITH SPONSOR.....	66
8.2 FDA QUESTIONS TO TEVA: FOLLOW-UP FROM DECEMBER 7 TH MEETING DISCUSSIONS	74
8.3 FDA PROPOSED SAFETY-RELATED LABELING FOR RASAGILINE.....	76

1. INTRODUCTION AND BACKGROUND

1.1 Data Sources

1.1.1 Sponsor Documents

1. NDA 21-641 (Rasagiline). Response to FDA Melanoma Comment. Prepared by Teva Neuroscience, Inc. Dated January 19, 2006.
2. NDA 21-641 (Rasagiline). Rasagiline Mesylate Final Safety Report. Prepared by Teva Neuroscience, Inc. Dated January 19, 2006.
3. NDA 21-641 (Rasagiline). Clinical Study Protocol (Phase IV Study). Prepared by Teva Neuroscience, Inc. Dated January 19, 2006.
4. NDA 21-641 (Rasagiline). Other Clinical Comments. Prepared by Teva Neuroscience, Inc. Dated January 19, 2006.
5. NDA 21-641 (Rasagiline). Amendment to Pending Application: Response to FDA Action Letter. Prepared by Teva Neuroscience, Inc. Dated November 4, 2004.
6. NDA 21-641 (Rasagiline). Briefing Package for meeting on December 7, 2005 to discuss melanoma in the Rasagiline Development Program. Prepared by Teva Pharmaceutical Industries. Received by FDA November 8, 2005.

1.1.2 FDA Documents

7. NDA 21-641 (Rasagiline). Clinical Review: NDA Primary Safety Review. Prepared by M. Lisa Jones, MD, MPH. Dated July 5, 2004.
8. NDA 21-641 (Rasagiline). NDA Approvable Letter – Misc. Deficiencies and Labeling Revisions Listed in Letter (First Action Letter). Prepared by the FDA¹ DNDP². Dated July 2, 2004.
9. NDA 21-641 (Rasagiline). NDA Approvable Letter – Misc. Deficiencies and Labeling Revisions Listed in Letter (Second Action Letter). Prepared by the FDA³ DNDP⁴. Dated August 4, 2005.
10. NDA 21-641 (Rasagiline). Clinical Review: Rasagiline Response to Approvable Letter Safety Review. Prepared by M. Lisa Jones MD, MPH. Dated July 27, 2005.
11. NDA 21-641 (Rasagiline). Memorandum of Meeting Minutes: December 7, 2005 Meeting with Teva. Prepared by the FDA DNP. Dated February 7, 2006.

The numbering in the list of documents above is used throughout this review to reference information adapted from the respective source document. For example, material in

¹ FDA=United States Food and Drug Administration

² DNDP=Division of Neuropharmacological Drug Products, Food and Drug Administration

³ FDA=United States Food and Drug Administration

⁴ DNDP=Division of Neuropharmacological Drug Products, Food and Drug Administration

Teva's "Response to FDA Melanoma Comment" would be designated by (Ref. 1) at the end of the sentence.

1.2 Review Content

Rasagiline (Azilect®) received an Approvable Action Letter from the DNDP² in July 2004. The sponsor submitted a Response to the Approvable Action Letter in January 2005. Teva's response addressed FDA concerns pertaining to ongoing safety issues, notably the investigation of melanomas within the rasagiline development program. In response to Teva's January 2005 submission, DNDP sent a second Approvable Action Letter in August 2005, asking that Teva address additional issues primarily related to the melanoma signal. Teva subsequently requested a meeting with the FDA to "answer any remaining questions on melanoma." The meeting occurred on December 7, 2005, and meeting minutes are presented in Attachment 1 of this review. Following the meeting, the FDA sent a list of questions to Teva, pursuant to discussions at the meeting.

This review addresses both the meeting briefing packet for the December 7th meeting (submitted in November 2005) and Teva's response to the FDA's follow-up questions from that meeting (submitted in January 2006). This document also reviews the other elements of the sponsor's January 2006 submission, which included:

- A protocol for a Phase IV melanoma study
- A safety update for the time period from the last data lock of July 31 2004 until the new data lock date of February 16 2005
- Comments on postmarketing rhabdomyolysis monitoring and a Phase IV QT interval study.

The January 2006 submissions were considered to constitute a complete response to the safety issues raised in the second Approvable Action Letter.

2. DECEMBER 7TH MEETING BRIEFING PACKET

2.1 Sponsor Introduction

In the Executive Summary of the sponsor's meeting briefing packet, Teva acknowledged uncertainty in interpreting the melanoma data collected in the rasagiline development program. However, Teva stated that the goal of the briefing package and meeting was to "convince the FDA that the signal observed with rasagiline is not sufficient in strength to preclude marketing." Teva asserted that the melanoma risk with rasagiline is no different than the risk with all Parkinson's disease (PD) drugs, as Teva believes PD itself is associated with melanoma. Teva referenced the following three Teva-sponsored studies in support of this assertion (Ref. 6, pg. 4):

Reviewer comment: *The study by Olsen and the EP001/EP002 cohort studies have been evaluated in prior FDA reviews. The study by Dr. Rigel has not been reviewed, as prior submissions contained insufficient information to evaluate the research.*

1. **Olsen et al.:** This Danish, linked-record study (N=14,031) found a two-fold increase in melanoma among PD patients.

Reviewer comment: *As assessed in prior FDA reviews, this study appears reasonably sound methodologically, with a large number of subjects, a long follow-up period and access to presumably high quality medical records databases.*

2. **Dr. Rigel's Study:** This study found a two-fold increased risk of PD among 919 melanoma patients compared to age- and gender-matched controls (2.9% vs. 1.3%, respectively).

Reviewer comment: *Teva characterized this study as using a case-control design. However, in the summary of Dr. Rigel's study in Attachment 4 of the sponsor's briefing packet, no concomitant North American control subjects without melanoma were described. Instead, the prevalence of PD among the melanoma patients was compared with the prevalence of PD among Rotterdam (Netherlands) residents as assessed by a study published in 1995⁵. In case-control studies, it is crucial that control subjects are selected from a population as similar as possible to the case population (except for the outcome studied). The lack of actual control subjects for comparison, or failing that, a literature study from a similar population, draws the results of this study into question. This is especially true as small changes (~1%) in PD prevalence can result in a doubling of PD in one group compared to another.*

In addition, although these findings may suggest some physiological common pathway for the two disorders, the observation of an elevated prevalence of PD in melanoma patients is otherwise not relevant to the question of interest here - whether people with PD are predisposed to melanomas.

Dr. Rigel presented a somewhat different version of this study at the 6th World Congress on Melanoma from September 6-10, 2005 in Vancouver, Canada.⁶ The study enrolled 862 melanoma patients (451 men, 411 women) and 862 age- and gender-matched controls through ten study sites in the United States. Among the melanoma patients, 2.9% (N=25) had developed PD (all age 64 or older), while only 1.3% (N=11) of the control subjects had done so (Relative Risk=2.2).

Reviewer comment: *In contrast to the study included by Teva in the Meeting Briefing Packet, the study described in the poster presentation above used 862 actual control subjects as the comparator group, and constituted a true case-control study. I consider the latter method as superior with regards to study conduct, and it is unclear*

⁵ De Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, Hofman A. Prevalence of parkinson's disease in the elderly: the Rotterdam study. *Neurology* 1995;45(12):2143-6.

⁶ The study was performed and presented at the meeting by Dr. Darrell Rigel, a Teva consultant. The poster presentation was entitled "Evaluation of the Association of Parkinson's Disease with Malignant Melanoma."

why Teva did not present this second study to the FDA. However, as noted in the reviewer comment above, I believe that the focus of this study (the development of PD in melanoma patients) is only peripherally related to the question of interest (the development of melanoma in PD patients).

3. **EP001 and EP002 Cohort Studies:** These sponsor-conducted melanoma screening studies in North America (EP002) and Israel (EP001) suggested an increased risk of melanoma in PD patients compared to the general population.

Reviewer comment: *The EP001 and EP002 studies examined melanomas in approximately 2000 PD patients (per study) through a single melanoma screening examination and collection of information on past skin cancers. These cohort studies are affected by the same difficulties in finding an appropriate comparator group as with the rasagiline development program. These difficulties include: lack of a comparator group undergoing active melanoma screening, lack of a comparator group in a closely geographically-matched area, and possible under-reporting to the comparator groups (an Israeli cancer registry and SEER⁷, respectively.) The safety review of these studies has primarily focused on the North American EP002 study, as melanoma rates vary by geographic location and an Israeli cohort (EP001) is therefore less relevant.*

Teva stated that, because the relationship between PD drugs and melanoma is unknown, rasagiline labeling should recommend periodic screening. Teva additionally stated that they believe that class labeling should be developed for all PD drug products. The sponsor noted that the recently approved ropinirole labeling appears generic in structure, from which they infer that FDA reviewers are also considering class labeling.

Reviewer comment: *The statement in the ropinirole labeling that the sponsor is referring to is provided below:*

“Melanoma: Some epidemiologic studies have shown that patients with Parkinson’s disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson’s disease or other factors, such as drugs used to treat Parkinson’s disease, was unclear. REQUIP is one of the dopamine agonists used to treat Parkinson’s disease. Although REQUIP has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using REQUIP for any indication should be made aware of these results and should undergo periodic dermatologic screening.”

⁷ SEER=Surveillance, Epidemiology and End Results Cancer Registry of the United States National Cancer Institute

2.2 Background

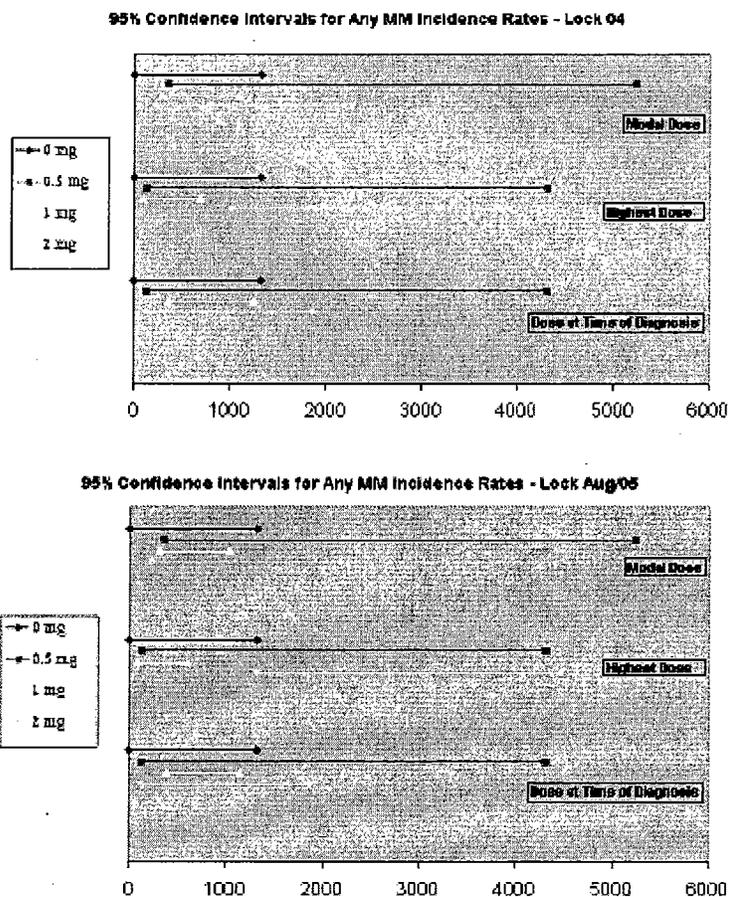
The sponsor was provided with a copy of the melanoma-relevant sections of the primary safety reviewer's report on Teva's Response to the Approvable Letter submission (for the first Approvable Letter issued July 2004). Section 2.3 and 2.4 below summarize Teva's comments in response to the FDA's melanoma review.

2.3 Dose-Response Analysis

Teva noted that, in addition to the surveillance bias and the long latencies associated with cancers, it was difficult to assess dose-response within TEMPO and PRESTO because many patients switched dose several times. Teva provided the following figures (based on absolute melanoma rates) as support for a lack of a dose-response trend (see subsequent tables 1, 2, and 3 for point estimates).

FDA Figure 1. Confidence Intervals for Melanoma Rates at 0 mg, 0.5 mg, 1 mg and 2 mg Rasagiline (Sponsor Figure 1, Ref. 6, pg. 8)

Figure 1. 95% Confidence intervals for any MM incidence rates



Point estimates for the confidence intervals in the figure above are shown in the following three tables.

FDA Table 1: Dose Response Calculation in Rasagiline Development Program, with Cases Assigned to Modal Dose (Adapted from Sponsor Post-Text Table 2, Ref. 6, pg.28)

	Cases Per 100,000 PYs (number observed and 95% CL)				
	0 mg (Subject-Years=420.9)	0.5 mg (Subject-Years=167.0)	1 mg (Subject-Years=1676.4)	2 mg (Subject-Years=468.3)	All (Subject-Years=2737.7)
Number of Invasive MM	0 (Obs=0, 95% CI=0-1106)	1198 (Obs=2, 95% CI=134.5-4324)	298 (Obs=5, 95% CI=96.1-696)	214* (Obs=1, 95% CI=2.8-1188)	292 (Obs=8, 95% CI=125.8-575.8)
Number of In-Situ MM	238 (Obs=1, 95% CI=3.1-1322)	599 (Obs=1, 95% CI=7.8-3331)	298 (Obs=5, 95% CI=96.1-696)	641 (Obs=3, 95% CI=128.8-1872)	365 (Obs=10, 95% CI=174.9-671.8)
Number of Any MM	238 (Obs=1, 95% CI=3.1-1322)	1796 (Obs=3, 95% CI=361.1-5248)	597 (Obs=10, 95% CI=285.6-1097)	854* (Obs=4, 95% CI=229.8-2187)	657 (Obs=18, 95% CI=389.5-1039)

Patient No. 164 was diagnosed after 2 months. Excluding this patient, the incidence rate for Number of Invasive MM is NA (95% CI=0-994.4), and for Any MM is 641 (95% CI=128.8-1872).

All 95% CI's were calculated via java applet, Open Source Statistics for Public Health, <http://openepi.com/Menu/OpenEpiMenu.htm> (One Person Time Rate)

FDA Table 2: Dose Response Calculation in Rasagiline Development Program, with Cases Assigned to the Highest Dose (Adapted from Sponsor Post-Text Table 3, Ref.6, pg.29)

	Cases Per 100,000 PYs (number observed and 95% CL)				
	0 mg (Subject-Years=420.9)	0.5 mg (Subject-Years=167.0)	1 mg (Subject-Years=1676.4)	2 mg (Subject-Years=468.3)	All (Subject-Years=2737.7)
Number of Invasive MM	0 (Obs=0, 95% CI=0-1106)	599 (Obs=1, 95% CI=7.8-3331)	119 (Obs=2, 95% CI=13.4-430.7)	1068* (Obs=5, 95% CI=344.1-2492)	292 (Obs=8, 95% CI=125.8-575.8)
Number of In-Situ MM	238 (Obs=1, 95% CI=3.1-1322)	599 (Obs=1, 95% CI=7.8-3331)	179 (Obs=3, 95% CI=36-522.8)	1068 (Obs=5, 95% CI=344.1-2492)	365 (Obs=10, 95% CI=174.9-671.8)
Any MM	238 (Obs=1, 95% CI=3.1-1322)	1198 (Obs=2, 95% CI=134.5-4324)	298 (Obs=5, 95% CI=96.1-696)	2135* (Obs=10, 95% CI=1022-3927)	657 (Obs=18, 95% CI=389.5-1039)

* Patient No. 164 was diagnosed after 2 months. Excluding this patient, the incidence rate for Number of Invasive MM is 854 (95% CI=229.8-2187), for Any MM is 1922 (95% CI=877-3648).

All 95% CI's were calculated via java applet, Open Source Statistics for Public Health, <http://openepi.com/Menu/OpenEpiMenu.htm> (One Person Time Rate)

FDA Table 3: Dose Response Calculation in Rasagiline Development Program, with Cases Assigned to Dose at Time of Diagnosis (Adapted from Sponsor Post-Text Table 4, Ref.6, pg.30)

	Cases Per 100,000 PYs (number observed and 95% CL)				
	0 mg (Subject-Years=420.9)	0.5 mg (Subject-Years=167.0)	1 mg (Subject-Years=1676.4)	2 mg (Subject-Years=468.3)	All (Subject-Years=2737.7)
Number of Invasive MM	0 (Obs=0, 95% CI=0-1106)	599 (Obs=1, 95% CI=7.8-3331)	358 (Obs=6, 95% CI=130.7-779)	214* (Obs=1, 95% CI=2.8-1188)	292 (Obs=8, 95% CI=125.8-575.8)
Number of In-Situ MM	238 (Obs=1, 95% CI=3.1-1322)	599 (Obs=1, 95% CI=7.8-3331)	358 (Obs=6, 95% CI=130.7-779)	427 (Obs=2, 95% CI=48-1542)	365 (Obs=10, 95% CI=174.9-671.8)
Any MM	238 (Obs=1, 95% CI=3.1-1322)	1198 (Obs=2, 95% CI=134.5-4324)	716 (Obs=12, 95% CI=369.5-1250)	641* (Obs=3, 95% CI=128.8-1872)	657 (Obs=18, 95% CI=389.5-1039)

* Patient No. 164 was diagnosed after 2 months. Excluding this patient, the incidence rate for Invasive is NA

(95% CI=0-994.4), and for Any MM is 427 (95% CI=48-1542).

All the 95% CI's were calculated via java applet, Open Source Statistics for Public Health, <http://openepi.com/Menu/OpenEpiMenu.htm> (One Person Time Rate)

Teva stated that Figure 1 demonstrated that rates in the 1 mg group are very similar to placebo, thus the results are not sensitive to the different case-allocation methods (“modal,” “maximal,” etc) and therefore considered quite reliable. When there is lower and variable exposure, as in the 0.5 and 2 mg groups, the rates as well as the upper CIs are higher, and the results are more sensitive to the calculation method (Ref. 6, pg. 9).

Reviewer comment: Teva verified⁸ that only the single placebo case (from the LARGO study) was included in the 0 mg group. In the Response to the Approvable Letter, the sponsor inappropriately included three cases of melanoma found prior to treatment initiation. The sponsor also verified that, in cases in which subjects received multiple doses, person-time was apportioned to each dose according to the time spent on that dose.¹

The sponsor noted that the relatively high rates and wide upper confidence limits in the 0.5 mg and 2 mg were mainly due to the low exposure at these doses. Teva stated that the modal dose approach was anticipated to result in lower rates in the 1 mg group, as most of the patients' exposure is with this dose.

Teva responded to a “finding of interest” in Dr. Katz’ “memo to the NDA file.” The memo indicated that the 2 mg group, which had the highest rate of melanomas, had the lowest melanoma surveillance. Teva stated that this is only true when the rate in the 2 mg group is calculated by “the highest dose” method. The memo also suggested that the melanoma rate for the 2 mg group may be artifactually low compared to the lower dose groups. Teva replied by stating it may be reasonable to assume that implementation of skin exams earlier in the experience for the 2 mg group would have resulted in additional melanomas being found, but it is not possible to calculate if this rate would have exceeded the rates for the 0.5 and 1 mg groups.

2.4 Immediate Vs. Delayed Start Analysis

⁸ Reply to FDA questions, received via electronic mail December 7, 2005

Teva provided the following responses to the FDA's immediate vs. delayed start analysis (Ref. 6, pg. 29-36).

1. Teva stated that if rasagiline promotes melanoma, and the six months delay in initiation of treatment with rasagiline has any significance, then the placebo (delayed start) patients would be expected to have significantly different melanoma rates than rasagiline (immediate start) patients. Teva maintained this is not the case, as comparison of each time strata from rasagiline start for both TEMPO and PRESTO demonstrated that the CIs for both groups overlap considerably (Table 4 below). In addition, comparison of the absolute rates with increased duration (up to and exceeding 24 months) for each study does not demonstrate a similar increase in incidence rate even within the immediate start group.

FDA Table 4: Incidence Rates of Melanoma per 1,000 Person Years in the Immediate and Delayed Start Groups by Time Strata from Time of Initial Rasagiline Exposure (Adapted from Sponsor Ref. 6, Post-Text Table 10, pg. 37)

Number of Melanomas Per Treatment Group	0-6 Months	6-12 Months	12-18 Months	18-24 Months	>24 Months
PRESTO Immediate	13.9 (Obs=2,N=313, PY=143.6, 95% CI=1.6-50.3)	26.9 (Obs=3,N=263, PY=111.5, 95% CI=5.4-78.6)	11.6 (Obs=1,N=196, PY=86.5, 95% CI=0.2-64.3)	0 (Obs=0,N=160, PY=74.3, 95% CI=0-62.3)	0 (Obs=0,N=139, PY=176.1, 95% CI=0-26.4)
PRESTO Delayed	17.9 (Obs=1,N=123, PY=56, 95% CI=0-299.4)	0 (Obs=0,N=86, PY=38.4, 95% CI=0-119.8)	0 (Obs=0,N=71, PY=33.8, 95% CI=0-135.9)	0 (Obs=0,N=63, PY=30, 95% CI=0-152.8)	0 (Obs=0,N=58, PY=46.4, 95% CI=0-99.4)
TEMPO Immediate	7.8 (Obs=1,N=266, PY=127.5, 95% CI=0.1-43.6)	8.4 (Obs=1,N=248, PY=119.4, 95% CI=0.1-46.6)	0 (Obs=0,N=212, PY=95.3, 95% CI=0-48.7)	11 (Obs=1,N=186, PY=90.8, 95% CI=0.1-61.3)	11.3 (Obs=7,N=178, PY=621.3, 95% CI=4.5-23.2)
TEMPO Delayed	0 (Obs=0,N=132, PY=62.9, 95% CI=0-73.5)	0 (Obs=0,N=111, PY=52.6, 95% CI=0-87.8)	0 (Obs=0,N=99, PY=48.6, 95% CI=0-94.9)	0 (Obs=0,N=95, PY=45.1, 95% CI=0-102.2)	6.8 (Obs=2,N=88, PY=294.5, 95% CI=0.8-24.5)
Total Immediate	11.1 (Obs=3,N=579, PY=271.1, 95% CI=2.2-32.3)	17.3 (Obs=4,N=511, PY=230.9, 95% CI=4.7-44.4)	5.5 (Obs=1,N=408, PY=181.8, 95% CI=0.1-30.6)	6.1 (Obs=1,N=346, PY=165.1, 95% CI=0.1-33.7)	8.8 (Obs=7,N=317, PY=797.4, 95% CI=3.5-18.1)
Total Delayed	8.4 (Obs=1,N=255, PY=118.9, 95% CI=0.1-46.8)	0 (Obs=0,N=197, PY=91, 95% CI=0-51)	0 (Obs=0,N=170, PY=82.4, 95% CI=0-56.2)	0 (Obs=0,N=158, PY=75.2, 95% CI=0-61.6)	5.9 (Obs=2,N=146, PY=340.9, 95% CI=0.7-21.2)

- PRESTO Immediate - Patient No. 613 was exposed 0.51 year was allocated by FDA to 0-6 months, should be allocated to 6-12 months.
- TEMPO Immediate - Patient No. 113 was exposed 0.93 year was allocated by FDA to 12-18 months, should be allocated to 6-12 months.
- TEMPO Immediate - Patient No. 246 was exposed 1.35 year was allocated by FDA to 12-18 months, should be allocated to 18-24 months.
- All 95% CIs were calculated via java applet, Open Source Statistics for Public Health. <http://openepi.com/Menu/OpenEpiMenu.htm> (One Person Time Rate)

The 95% confidence intervals of the TEMPO Immediate >24 months exposure group and TEMPO Delayed >24 months exposure group overlap (4.5-23.2 for TEMPO Immediate and 0.8-24.5 for TEMPO Delayed).Comparing 2 person-time rates of TEMPO Immediate >24 months exposure group and TEMPO Delayed >24 months exposure group, using Fisher Exact test, yielded a p-value of 0.4066. Calculated via java applet, Open Source Statistics for Public Health, <http://openepi.com/Menu/OpenEpiMenu.htm> (Two Person Time Rates)

The 95% confidence intervals of the Total Immediate >24 months exposure group and Total Delayed >24 months exposure group overlap (3.5-18.1 for Total Immediate and 0.7-21.2 for Total Delayed).Comparing 2 person-time rates of Total Immediate >24 months exposure group and Total Delayed >24 months exposure group, using Fisher Exact test, yielded a p-value of 0.4642. Calculated via java applet, Open Source Statistics for Public Health, <http://openepi.com/Menu/OpenEpiMenu.htm> (Two Person Time Rates)

2. Teva noted that cases in the immediate start group are fairly widely distributed with regards to rasagiline exposure before melanoma diagnosis, ranging from 3 months to 65 months. Teva stated that it is difficult to conceive that the six initial months of treatment (whether placebo or rasagiline) had any effect on melanomas diagnosed five to six years later.

Reviewer comment: *Although some cases were diagnosed after considerable rasagiline exposure, 10 of the 17 cases had less than two year's exposure.*

Teva stated that out of a total of 14 melanomas diagnosed *after* the placebo-controlled phase, approximately one third are expected in the placebo group by chance alone, since the randomization was 2:1 (rasagiline:placebo). Teva noted that the three delayed cases and 11 immediate start patients are not significantly different than what would be expected by chance (4.7 delayed cases, 9.3 immediate cases; p 0.26). Of the cases diagnosed during the placebo-controlled phase, in TEMPO only one rasagiline-treated patient was diagnosed with melanoma. This case involved an advanced and likely pre-existing lesion diagnosed after only two months rasagiline treatment. Teva stated it is not plausible that this melanoma was affected by the brief rasagiline exposure. In PRESTO, three rasagiline-treated patients were diagnosed, which does not differ from chance given the 2:1 (rasagiline:placebo) randomization (Expected 2 cases in the rasagiline group and 1 case in the placebo group; p 0.30) (Ref. 6, pg. 9-10).

2.5 Additional Sponsor Points

2.5.1 Increased Rates of Melanoma in the Rasagiline Development Program Compared to Other PD Development Programs

Teva maintained that comparison of melanomas within the rasagiline development program to other PD development programs is confounded by the dermatologic screening examinations and other melanoma awareness activities (such as a "Dear Doctor" letter sent to site investigators) within the rasagiline development program. Teva stated that this detection bias alone could have resulted in a higher rate of melanomas, as no other development program had such measures.

Reviewer comment: *When the comparison is restricted to only those melanomas within the rasagiline development program diagnosed prior to institution of the screening program, the rasagiline melanoma rate is still the highest of all the development programs (5.8 per 1,000 person-years in the rasagiline development program, compared to 1.6 in the pramipexole development program, 1.3 in the tolcapone development program, 0.3 in the ropinirole development program, and no melanomas reported in the pergolide and entacapone development programs). During the December 7th meeting, sponsor representatives countered that:*

- *One of the pre-screening melanomas is doubtfully related to rasagiline due to a brief (two months) exposure.*

- *Some melanoma awareness activities (such as a “Dear Health Care Professional” letter to site investigators) preceded the institution of melanoma screening and may have heightened melanoma detection.*

A post-meeting question was sent to the sponsor for additional information on the sponsor position regarding the pre-screening melanomas. This issue, as well as the comparison to the melanoma rate in other PD development programs, is discussed further in Section 3.3 of this review.

Teva again noted that one of the pre-screening cases was an apparently pre-existing (as per patient history), Clark’s level IV lesion diagnosed two months after beginning rasagiline. Teva maintained that a causal relationship between such an advanced lesion and the brief rasagiline exposure is doubtful (Ref. 6, pg. 11).

2.5.2 Melanoma Rate in the Rasagiline North American Clinical Program and Comparison to Control

Teva proposed the following additional approach to assess the number of melanomas without the benefit of a concurrent control group. Teva stated that at the time of the NDA submission (data lock July 2003), most of the exposure to rasagiline was in North American active treatment studies (TEMPO and PRESTO)(1457 PYs rasagiline vs. 137 PYs placebo). There were 16 melanomas in the rasagiline group, for a ratio of **1:91** (16 cases/1457 PYs, or 1.1%). With continuing rasagiline exposure, the ratio was **1:109** (0.9%)(data lock 2004) and **1:122** (0.8%)(data lock August 2005). Teva concluded that the rate of melanoma decreased with continued exposure, which is inconsistent with the behavior of a carcinogen (Ref. 6, pg. 11-12).

***Reviewer comment:** Teva does not comment on the effect of subject drop-out over time. Subjects with prior melanomas (either within the study or previously) may have discontinued the study at a greater rate than other subjects following the melanoma alerts and screening. This could reduce the number of subjects at greater risk for melanoma over time. In addition, melanomas occurring after subject discontinuation are most likely not captured by the development program adverse event monitoring. This would also decrease the number of melanomas among subjects continuing in the study.*

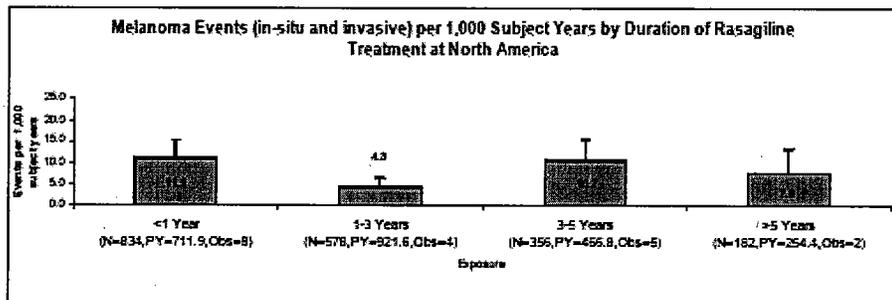
Teva further outlined the following line of reasoning. The sponsor stated that conservatively assuming melanoma rate of 1:100 (equal for rasagiline and placebo treatment) and a Poisson distribution, 1.37 cases would be expected in the placebo group. Under these assumptions, the probability of having no cases in the placebo arm is 0.25, so the hypothesis of equal rates cannot be rejected. Assuming a rate of 1:120, this would yield a probability of 0.32 to have 0 cases in the placebo arm (Ref. 6, pg. 12).

2.5.3 Melanoma Incidence Rate by Duration of Exposure

Teva stated that if rasagiline is a true carcinogen, one would expect the rate of melanoma to increase with longer exposure. Teva provided the following figure as evidence to the contrary:

FDA Figure 2. Melanomas by Rasagiline Treatment Duration (Sponsor Figure 2, pg. 13)

Figure 2. Incidence of melanoma events by duration of rasagiline treatment



Reviewer comment: Regarding case and person-year allocation to the different strata, Teva stated that “person-years and cases are allocated to corresponding duration stratum and the incidence is computed.” During the December 7th meeting, Teva verified that person-time in Figure 2 was apportioned to each time strata to which a subject contributed data.

As with the reviewer comment in Section 2.5.2 above (North American Clinical Program and Comparison to Control), Teva did not comment on the effect of discontinuing subjects. The substantial loss of patients out of the cohort over time makes the sponsor’s argument less compelling.

Teva observed that eight melanomas were diagnosed within the first year of exposure. Teva noted that although the rate of melanomas appears to increase after 5 years when in situ and invasive melanomas are examined separately, this increase is not statistically significant. Teva reiterated that the initiation of melanoma screening, begun in November 2001, confounded the assessment of melanoma rates over time (Ref. 6, pg. 15).

2.5.4 Comparison of EP002 to the Rasagiline Development Program

Reviewer comment: This comparison differs from the comparison of rates in EP002 to background rates as per the American Academy of Dermatology melanoma screening study, performed in the previous review (Response to the Approvable Letter). As stated during the December 7th meeting, the sponsor did not comment on the EP002/AAD comparison due to time constraints.

Of the 2106 patients screened in EP002, 20 in situ and 4 invasive melanomas were found (1.1%). Teva noted that this is similar to the proportion observed at the first screening in the rasagiline development program (1.2% in rasagiline and 1.1% placebo). The sponsor acknowledged that methodological differences make the comparison less than ideal, but stated that melanoma risks in the rasagiline program (only patients with a first skin exam) and EP002 (patients diagnosed at their first skin exam) are comparable (Mid-P Exact test for invasive melanomas $p=0.308$, for in situ $p=0.733$, for any melanoma $p=0.838$) (Ref. 6, pg. 16).

Reviewer comment: *As would be appropriate, the 24 EP002 melanomas included only those diagnosed during the single study screening, and not the retrospective melanomas prior to joining the study, which the sponsor also collected information on.*

2.5.5 Detection Bias: Non-Melanoma Skin Cancers

Given that skin exams began when only a small amount of control experience had accumulated, the sponsor stated it is not surprising that most cases of melanoma and non-melanoma skin cancer occurred in the rasagiline treatment group. Teva presumed that the detection bias introduced by the active dermatologic examinations applied to both melanoma and non-melanoma skin cancers. The sponsor observed that several types of non-melanoma skin cancers were detected at higher rates than expected based on experience in other PD development programs or in the published literature.⁹ As with melanomas, there was a marked increase in non-melanoma skin cancers immediately following the introduction of dermatologic screening (Ref. 6, pg. 17).

Reviewer comment: *The sponsor again notes that the relative increase in melanomas with rasagiline treatment, as compared to other development programs and the placebo group, could be attributable to a surveillance bias due to dermatologic screening. Although there may be some validity to this statement, the rate of melanomas was also highest in the rasagiline development program (as compared to other development programs) when only prescreening melanomas and exposures were used to calculate the rate. (See Section 3.3 of this review for further details).*

2.5.6 Non-Clinical

In response to FDA concerns regarding a mouse carcinogenicity study, Teva asserted that the findings are minimally relevant to a human population treated at therapeutic doses. Teva summarized their interpretation of the carcinogenicity data as follows (Ref. 6, pgs. 19-21):

⁹ Sponsor reference: Harris et al., Journal of the American Academy of Dermatology (2001). Non-melanoma skin cancer background rate reported as about 1 per 100 person-years for a 60-69 year old age group.

- In the mouse carcinogenicity study, doses of 1, 15 and 45 mg/kg/day were administered, significantly higher than the recommended human dose.
- A higher incidence of combined bronchiolar/alveolar adenoma and/or carcinoma was observed in the intermediate and high dose groups. The rasagiline exposure at the 1 mg/kg dose considered the NOEL in this study demonstrated an exposure ratio of six times the human exposure at therapeutic dose. Teva noted that there is a 15-fold gap between the low and intermediate doses, and the true NOEL may be a much higher dose.
- Teva also raised the possibility that the findings are due to a mouse specific metabolite. The sponsor previously stated that the metabolic profile of various animal species as well as humans were comparable. Upon further investigation Teva now states a minor metabolite, with a yet unknown structure, is found in the plasma and urine of treated mice. This metabolite was also found in rats, at a much lower level, but not in humans.

Reviewer comment: *In his preliminary review⁴, Dr. Paul Roney responded as follows to Teva's statement on the presence of minor mouse metabolite.*

“This is highly speculative. The sponsor has not provided any data (not even plasma levels in mice) to support their speculation that this unknown metabolite is the source of the positive genotoxicity and carcinogenicity findings. The sponsor should come back when they have more data to support this argument.”

- Tests in the mouse micronucleus (rasagiline alone and with levodopa) and unscheduled DNA synthesis tests in rat liver cells were negative.

Teva maintained that the positive findings in some of the in vitro genotoxicity studies do not represent the action of a direct strong mutagen, but instead a weak clastogen for which a safety margin can be determined. The sponsor outlined their thoughts on the in vitro studies as below:

- Rasagiline was clastogenic in the in vitro chromosomal aberration assay only in media with gentamicin and without glutathione. Other assays were negative.
- Maximal plasma levels in patients are a million times lower than the in vitro levels showing a clastogenic effect.

Reviewer comment: *Dr. Paul Roney, the pharmacology-toxicology reviewer, wrote the following in his preliminary review¹⁰ regarding the two preceding sponsor assertions:*

“This reviewer has previously examined the Sponsor's arguments in his NDA review and found them unconvincing. The sponsor is attempting to explain away three positive chromosomal aberration studies conducted with gentamycin in the media.

¹⁰ Received via electronic mail, December 5, 2005

Gentamycin is a standard antibiotic used in tissue media and the sponsor needs to explain why we should ignore these three positive tests. In addition, I would not classify a 7% chromosome aberration rate (as compared to 1% and 0% in negative and solvent controls, respectively) as being weak. Finally, the sponsor needs to explain why glutathione (which is supposed to protect against genotoxicity) could increase the genotoxicity of rasagiline.”

- *Mouse Lymphoma tk Assay:* Sizing of colonies in a mouse lymphoma tk assay was performed, and the results indicated that the increased number of colonies was predominantly due to small colonies, as opposed to large colonies. The sponsor stated that small colonies are associated with gross chromosomal damage, whereas large colonies are associated with changes within genes.

Reviewer comment: *Dr. Paul Roney stated in his preliminary review⁴ of the pharmacotoxicology data that:*

“The sponsor bases this statement on the increased ratio of small to large colonies at the high doses in the mouse lymphoma assay. However, if one examines the actual number of large and small colonies detected in this assay, there are a 1.7 to 2.8 fold increases in large colonies in these studies...It follows that there is evidence that rasagiline has mutagenic as well as clastogenic potential in mammalian cells.”

- The positive results in the absence of the S9 metabolic system in this assay was obtained only at the highest dose tested, which was so cytotoxic that relative growth was inhibited by 80%. In addition, the increase just exceeded the minimum needed for a positive result.

Reviewer comment: *Dr. Paul Roney, the pharmacology-toxicology reviewer reached the following preliminary conclusion⁴ regarding the preclinical data presented in the meeting briefing packet:*

“The sponsor emphasizes the data supporting their position (negative Ames, in vivo micronucleus tests) while dismissing data that do not support their position (3 positive in vitro chromosomal aberration assays, positive mouse lymphoma assay, increased lung tumors the in mouse carcinogenicity assay (both sexes). The Sponsor’s does not provide adequate justification to dismiss these findings. This reviewer concludes that rasagiline is genotoxic in mammalian in vitro systems and carcinogenic in both male and female mice (increased combined lung adenoma/carcinoma).”

2.6 Sponsor-Proposed Melanoma Risk Management Program

Teva proposed that a risk management program accompany the launch of rasagiline in the United States. Based on the sponsor’s understanding of FDA guidances, Teva stated the program will address the following:

1. Assessing rasagiline's benefit-risk balance
2. Developing and implementing tools to minimize risks while preserving benefits
3. Evaluating tool effectiveness and reassessing the benefit-risk balance
4. Adjusting, as appropriate, the risk minimization tools to further improve the benefit-risk balance

Teva planned action in the following areas: enhanced safety monitoring, risk minimization and large simple randomized controlled Phase IV trial. Each is discussed in turn in the sections below.

2.6.1 Enhanced Safety Monitoring

Teva stated that they will "ensure intensive data collection" for melanomas. Teva pledged to conduct a "real-time" review of all melanoma reports collected from all sources (spontaneous, post-marketing activities, clinical studies and medical literature), verifying the information obtained for completeness and requesting additional data as needed. For each melanoma report, Teva specified that a special investigation using a pre-defined questionnaire will be performed. If needed, a safety officer from Teva will contact the reporting health care professional by phone. Teva stated that a special melanoma section will be part of all PSUR¹¹s (Ref. 6, pg. 23).

2.6.2 Risk Minimization Program

Teva stated that the goal of the risk minimization program "is to ensure that PD health care practitioners, patients and their caretakers are aware of the association between melanoma and PD, and the ensuing need for periodic skin exams." Teva described the components of the risk minimization program as labeling and a public education campaign (Ref. 6, pg. 24).

2.6.3 Labeling

Reviewer comment: *The safety relevant labeling for rasagiline proposed by the DNP is presented in Attachment 8.3 of this review.*

Teva stated that the rasagiline labeling should contain the following:

- 1.

Reviewer comment: *I would prefer*

¹¹ PSUR = Periodic Safety Update Report
Clinical Review
M. Lisa Jones, MD, MPH
NDA 21-641
Rasagiline (Azilect ®)

2. A statement indicating that some epidemiologic studies demonstrate that patients with PD have a higher risk of developing melanoma than the general population

Reviewer comment: Although a few epidemiologic studies have found an association between PD and melanoma, this association is certainly not well established.

3. A recommendation that patients using rasagiline undergo periodic screening

The sponsor further stated that labeling will be updated as necessary to incorporate additional information from post-marketing surveillance (Ref. 6, pg. 23-24).

Reviewer comment: The results of the Phase IV melanoma study (described in Sections 2.7 and 4 of this review) will also provide important information for labeling.

2.7 Large Simple Randomized Controlled Trial (Phase IV)

Teva described the study as comparing melanoma rates in PD patients exposed and unexposed to rasagiline. Subjects will be randomized into two treatment groups:

1. Rasagiline with/without other available PD medications
2. Any PD drug(s) excluding rasagiline

Teva stated they will investigate the feasibility of the trial design and provide additional information in advance of the meeting. Trial design will be further discussed during the meeting with the DNP.

Reviewer comment: A large, simple trial, such as that described above, provides the most feasible opportunity for elucidating any relationship between rasagiline and

Clinical Review

19

M. Lisa Jones, MD, MPH

NDA 21-641

Rasagiline (Azilect ®)

melanoma. If Teva would like to further investigate the link between PD and melanomas, they could add a third, age-matched group of subjects without PD.

2.8 Sponsor Summary and Conclusions

In their summation, Teva reiterated the following points made in the current and previous submissions:

- Analyses do not show an increase in melanomas with long-term rasagiline use.
- There is no evidence of an early increase in melanoma incidence soon after starting rasagiline that could suggest growth activation of an existing lesion.
- There is no evidence of a dose-response trend.
- Detection bias due to the dermatologic screening program and the increased risk of melanoma in PD patients explains the relative increase in melanoma as compared with SEER or other PD development programs.
- As support for the preceding, Teva noted that non-melanoma skin cancers also increased after the dermatologic screening program began and occurred at a greater than expected rate compared to the general population.
- Melanomas in SEER are underreported.
- Results of genotoxicity testing are not indicative of direct mutagen activity.
- Carcinogenicity in rats did not reveal an increase in tumors at doses with exposures 84 (male rats) and 399 (female rats) times greater than the recommended clinical dose in humans.
- The mouse study did demonstrate higher incidences of combined lung adenoma/carcinoma in the intermediate and high dose groups, but the lowest dose associated with tumors produced an AUC in the mouse about 170 times that seen in humans at therapeutic doses. Even this finding may be due to a specific mouse metabolite not found in humans.

Teva concluded that “the uncertainty that exists with rasagiline” does not rise to the level “that would preclude marketing.” Based on the belief that PD patients are at increased risk for melanoma, Teva recommended treating PD as “a major melanoma risk factor.” Teva therefore intends to:

- Include a statement in the rasagiline labeling recommending periodic screening (Teva also encouraged melanoma class labeling for all PD drugs.)(Section 2.6.3 above)
- Implement a public education campaign (Section 4.2.2 above)
- Conduct a large, simple, Phase IV trial (See Section 4.3 above)

Reviewer comment: *My comments on the sponsor assertions regarding the analysis and their proposed actions concerning melanoma risk are included in their respective sections of this review, and are not re-stated in full here.*

Despite considerable analysis of the development program data, uncertainty regarding the causal role of rasagiline in melanoma development remains. Some evidence exists

supporting an association between melanoma and PD or its treatments. The primary evidence of this is the comparison of the sponsor's EP002 PD cohort study to melanoma prevalence data from the American Academy of Dermatology (AAD) skin cancer screening program. This comparison found a five-fold higher rate of melanoma among the EP002 PD population than would be expected from the melanoma rates in the AAD screening program.

I continue to believe that a large, simple trial represents the best method for understanding any relationship between rasagiline and melanoma. Until such a study is completed, the rasagiline labeling statement should describe the development program data and recommend screening. Given the continued uncertainty regarding rasagiline and melanoma, postmarketing surveillance should be rigorous.

3. SPONSOR RESPONSE TO POST-MEETING FDA QUESTIONS

The FDA sent the following questions to Teva to collect follow-up information on issues discussed during the December 7th meeting (the meeting minutes are contained in Attachment 8.1 and the follow-up questions are contained in Attachment 8.2 of this review.) Section 3 below reviews Teva's responses to these questions.

3.1 Melanoma Risk Factor Comparison in Continuing and Discontinuing Subjects

3.1.1 FDA Question to Teva

“Please submit an analysis comparing melanoma risk factors and other melanoma-relevant demographic factors (notably, age and sex) for the cohorts of continuing and discontinuing subjects in TEMPO and PRESTO (for each study separately). For TEMPO, in particular, another melanoma-relevant factor that should be compared for the continuation and discontinuation cohorts is the addition of L-dopa therapy.

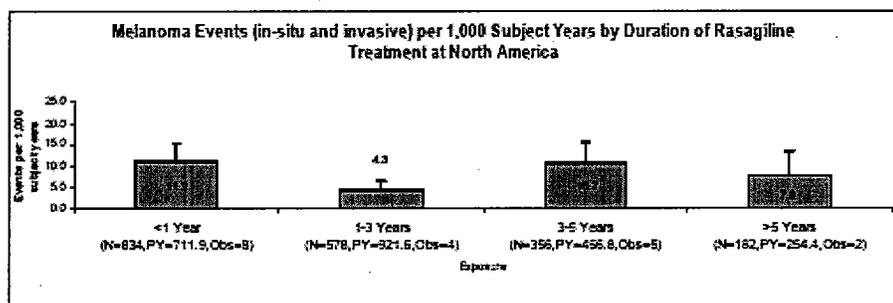
Due to screening initiation and other melanoma awareness activities, the comparison should be performed at various time points, assessed as both time from study start (for example, at six months, 12 months, 24 months, 36 months) and time by calendar year (for example, all subjects, regardless of time in study, before and after commencement of dermatologic screening.)”(Ref. 11)

Reviewer comment: *The question above arose from a review of a plot of melanoma incidence by duration of rasagiline exposure, submitted by Teva as part of the briefing packet for the December 7, 2005 meeting with the DNP (See Section 2.5.2 of this review). The plot (shown below) showed the highest rate of melanoma (11.2/1000 PYs) in the lowest exposure strata, followed by lower rates with continued exposure. There was a concern that this pattern may have arisen or been contributed to by subjects with higher*

risk for melanoma discontinuing the study over time, perhaps as a result of the amended informed consent alerting subjects to the occurrence of melanomas within the trial. The request was therefore made to Teva to quantitatively compare the risk factors for continuing and discontinuing subjects within the rasagiline development program.

FDA Figure 3: Melanomas by Rasagiline Treatment Duration (Sponsor Figure 2, Ref. 6, pg. 13)

Figure 2. Incidence of melanoma events by duration of rasagiline treatment



3.1.2 Sponsor Response with Reviewer Comments

3.1.2.1 Methods

The sponsor compared continuing and discontinuing¹² rasagiline-treated patients with regard to the following factors: age, gender, PD duration, melanoma risk factors and L-dopa treatment (for the TEMPO study only). Subjects diagnosed with melanoma were excluded from the analyses, and separate analyses were performed for the TEMPO (monotherapy) and PRESTO (levodopa adjunct) studies (Ref. 1, pg. 5).

Teva performed the continuing/discontinuing subject comparison using two methods to examine time:

1. **Calendar Time:** Teva noted that because dermatologic screening did not begin until several months after the study protocol amendment in September 2001, first subject screenings occurred over a broad range of calendar time. The sponsor divided calendar time into pre- and post-screening periods as follows:
 - a) The time *before* the first dermatology exam for 90% of PRESTO and TEMPO subjects (From study start to May 31, 2002).
 - b) The time *after* the first dermatology exam for 90% of PRESTO and TEMPO subjects (From June 1, 2002 to the most recent data lock of August 28, 2005).

¹² In this analysis, Teva defined discontinuation as early withdrawal or a decision not to enter the extension study.

2. **Time at different points (t) from rasagiline start** (t = 6 months, 12 months, 24 months, 36 months, etc.). For each time point, Teva defined the Discontinuation Cohort as all patients who discontinued before t months. The Continuation Cohort was defined as patients from all time intervals who were ongoing at the recent August 2005 data lock. Patients who discontinued before the August 2005 data lock and who were treated with rasagiline for at least t months were included in the Continuation Cohort only at time intervals until t.

Teva stated that, to reduce bias in the comparison between the two cohorts, age and PD duration were measured as of rasagiline start.

3.1.2.2 Results

Age by Calendar Time

Based upon the tables below, Teva observed that the mean age in the Continuation and Discontinuation cohorts was similar, although it was slightly higher in the Discontinuation Cohort (Ref. 1, pg. 6).

FDA Table 5: Mean Age by Calendar Time for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Tables 5 and Table 7. Appendix A, Ref. 1)

Study	Time Period	Age in Continuation Cohort	Age in Discontinuation Cohort
TEMPO	Nov. 7, 1997 to May 31, 2002	Mean: 61.0 Median: 62.7 Range: 33-79	Mean: 61.8 Median: 62.9 Range: 32-92
	June 1, 2002 to August 28, 2005	Mean: 64.5 Median: 65.9 Range: 41-82	Mean: 65.2 Median: 65.0 Range: 36-83
	December 4, 2000 to May 31, 2002	Mean: 62.7 Median: 63.1 Range: 33-84	Mean: 63.6 Median: 65.0 Range: 43-78
PRESTO	June 1, 2002 to August 28, 2005	Mean: 63.1 Median: 62.8 Range: 40-84	Mean: 64.4 Median: 64.5 Range: 33-82

Age by Time from Study Start

Teva noted that the mean age at rasagiline start was similar over time, and interpreted this as meaning that the Continuation Cohort was representative of all rasagiline-treated patients in TEMPO and PRESTO. Teva stated that the highest exposure interval (0 to 96 months for TEMPO and 0 to 60 months for PRESTO) represented the overall comparison for the Continuation and Discontinuation cohorts. The sponsor asserted that this

comparison demonstrated no meaningful difference in the mean age between the two cohorts (Ref. 1, pg. 6).

FDA Table 6: Mean Age by Time from Study Start for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Table 6 and Table 8, Appendix A, Ref. 1)

Study	Time Period	Age in Continuation Cohort	Age in Discontinuation Cohort
TEMPO	0-6 Months	Mean: 61.1 Median: 62.7 Range: 32-79	Mean: 63.4 Median: 65.0 Range: 39-92
	0-12 Months	Mean: 60.9 Median: 62.6 Range: 32-79	Mean: 63.0 Median: 64.6 Range: 37-92
	0-24 Months	Mean: 61.0 Median: 62.7 Range: 33-79	Mean: 62.2 Median: 63.1 Range: 32-92
	0-36 Months	Mean: 60.9 Median: 62.4 Range: 33-79	Mean: 62.1 Median: 63.4 Range: 32-92
	0-48 Months	Mean: 61.3 Median: 62.9 Range: 33-79	Mean: 61.5 Median: 62.7 Range: 32-92
	0-60 Months	Mean: 61.0 Median: 62.7 Range: 39-79	Mean: 61.7 Median: 62.9 Range: 32-92
	0-96 Months	Mean: 60.9 Median: 62.7 Range: 39-79	Mean: 61.7 Median: 62.9 Range: 32-92
	PRESTO	0-6 Months	Mean: 63.2 Median: 63.4 Range: 33-84
0-12 Months		Mean: 63.2 Median: 63.5 Range: 33-84	Mean: 63.9 Median: 64.1 Range: 42-81
0-24 Months		Mean: 62.8 Median: 62.6 Range: 40-84	Mean: 64.1 Median: 64.9 Range: 33-82
0-36 Months		Mean: 62.6 Median: 62.7 Range: 40-84	Mean: 64.1 Median: 64.6 Range: 33-82
0-48 Months		Mean: 62.8 Median: 62.7	Mean: 63.9 Median: 64.3

	Range: 40-84	Range: 33-82
0-60 Months	Mean: 62.8	Mean: 63.9
	Median: 62.7	Median: 64.3
	Range: 40-84	Range: 33-82

Reviewer comment: The age in the Discontinuation Cohort is consistently higher than in the Continuation Cohort (regardless of whether mean or median is considered), although the differences are small (generally less than two years). Whether this small difference represents a meaningful elevation in melanoma risk is uncertain, but the general trend is for skin cancer risk to increase with age.

Gender by Calendar Time

Teva stated that, in general, the percent of males was similar in the Continuation and Discontinuation cohorts, although it was minimally higher in the Continuation Cohort.

FDA Table 7: Gender by Calendar Time for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Tables 9 and Table 11, Ref. 1)

Study	Time Period	Gender in Continuation Cohort	Gender in Discontinuation Cohort
TEMPO	Nov. 7, 1997 to	% Male: 65	% Male: 61
	May 31, 2002	% Female: 35	% Female: 39
	June 1, 2002 to	% Male: 66	% Male: 60
	August 28, 2005	% Female: 34	% Female: 40
PRESTO	December 4, 2000 to	% Male: 68	% Male: 63
	May 31, 2002	% Female: 32	% Female: 37
	June 1, 2002 to	% Male: 73	% Male: 60
	August 28, 2005	% Female: 27	% Female: 40

Gender by Time From Study Start

Gender by time from study start is summarized in the following table.

FDA Table 8: Gender by Time from Study Start for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Table 10 and Table 12, Ref. 1)

Study	Time Period	Age in Continuation Cohort	Age in Discontinuation Cohort
TEMPO	0-6 Months	% Male: 64 % Female: 36	% Male: 56 % Female: 44
	0-12 Months	% Male: 64	% Male: 60

	0-24 Months	% Female: 36 % Male: 65	% Female: 40 % Male: 60
	0-36 Months	% Female: 35 % Male: 65	% Female: 40 % Male: 62
	0-48 Months	% Female: 35 % Male: 65.7	% Female: 38 % Male: 61
	0-60 Months	% Female: 34.3 % Male: 66	% Female: 39 % Male: 62
	0-96 Months	% Female: 34 % Male: 66	% Female: 38 % Male: 61
PRESTO	0-6 Months	% Female: 34 % Male: 68	% Female: 39 % Male: 54
	0-12 Months	% Female: 32 % Male: 69	% Female: 46 % Male: 60
	0-24 Months	% Female: 31 % Male: 68	% Female: 40 % Male: 63
	0-36 Months	% Female: 32 % Male: 72	% Female: 37 % Male: 61
	0-48 Months	% Female: 28 % Male: 73	% Female: 39 % Male: 61
	0-60 Months	% Female: 27 % Male: 73	% Female: 39 % Male: 61
		% Female: 27	% Female: 39

Reviewer comment: *As seen with the age comparison, there is a consistent difference between the Continuation and Discontinuation cohorts with respect to gender; the percent of female subjects is about five to ten percent higher in the Discontinuation Cohort. Teva does not note or address the consistent differences in gender distribution observed in both the TEMPO and PRESTO trials.*

In the American Academy of Dermatology screening program data, the rate of melanoma in persons ages 55 to 64 was roughly twice as high in men than women, although this gender difference narrows with increasing age. This would suggest that, as predicted by gender alone, the melanoma risk in the Discontinuation Cohort would be lower than in the Continuation Cohort.

PD Duration

Based on the tables below, Teva characterized the mean PD duration in the Continuation and Discontinuation cohorts as similar over time, with slightly higher PD durations seen occasionally in the Continuation Cohort. Teva concluded that, because the mean PD duration at rasagiline start remained similar over time, the Continuation cohort is not significantly altered by the discontinuations (Ref. 1, pg. 11).

FDA Table 9: PD Duration by Calendar Time for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Tables 13 and Table 15, Appendix A, Ref. 1, Pg. 30)

Study	Time Period	PD Duration in Continuation Cohort	PD Duration in Discontinuation Cohort	
TEMPO	Nov. 7, 1997 to May 31, 2002	Mean: 1.3 Median: 0.9	Mean: 1.0 Median: 0.7	
	June 1, 2002 to August 28, 2005	Mean: 5.0 Median: 4.6	Mean: 4.8 Median: 4.5	
	PRESTO	December 4, 2000 to May 31, 2002	Mean: 9.0 Median: 8.1	Mean: 9.4 Median: 8.5
		June 1, 2002 to August 28, 2005	Mean: 10.0 Median: 8.7	Mean: 9.4 Median: 8.4

FDA Table 10: PD Duration by Time from Study Start for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Table 14 and Table 16, Appendix A, Ref. 1, pg. 30)

Study	Time Period	PD Duration in Continuation Cohort	PD Duration in Discontinuation Cohort
TEMPO	0-6 Months	Mean: 1.2 Median: 0.8	Mean: 1.1 Median: 0.9
	0-12 Months	Mean: 1.2 Median: 0.8	Mean: 1.0 Median: 0.7
	0-24 Months	Mean: 1.2 Median: 0.8	Mean: 1.1 Median: 0.7
	0-36 Months	Mean: 1.2 Median: 0.9	Mean: 1.1 Median: 0.7
	0-48 Months	Mean: 1.3 Median: 0.9	Mean: 1.0 Median: 0.7
	0-60 Months	Mean: 1.3 Median: 0.9	Mean: 1.0 Median: 0.7
	0-96 Months	Mean: 1.3 Median: 0.9	Mean: 1.1 Median: 0.7
	PRESTO	0-6 Months	Mean: 9.4 Median: 8.2
0-12 Months		Mean: 9.7 Median: 8.4	Mean: 8.8 Median: 8.1
0-24 Months		Mean: 9.7 Median: 8.3	Mean: 9.1 Median: 8.4
0-36 Months		Mean: 9.5 Median: 8.4	Mean: 9.3 Median: 8.3

0-48 Months	Mean: 9.7 Median: 8.4	Mean: 9.2 Median: 8.2
0-60 Months	Mean: 9.7 Median: 8.4	Mean: 9.2 Median: 8.2

Melanoma Risk Factors

Teva stated that collection of Melanoma Risk Factors (MRFs)¹³ began after the TEMPO and PRESTO studies had already commenced. For this reason, data are available for only about 50% of TEMPO patients and for approximately 75% of PRESTO patients.

Therefore, patients who discontinued before implementation of MRF collection do not have data, and were not included in the comparison. Teva clarified that this is why no data is available for the Discontinuation Cohort up to one year and data is available for only three patients between one and three years. Teva believed that, based on the tables below, there were no substantial differences in melanoma risk factors between the Continuation and Discontinuation cohorts at any time point (Ref. 1, pg. 13).

FDA Table 11: Melanoma Risk Factors by Calendar Time for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Tables 17 and Table 19, Appendix A, Ref. 1)

Study	Time Period	MRFs in Continuation Cohort	MRFs in Discontinuation Cohort
TEMPO	Nov. 7, 1997 to May 31, 2002	Mean: 2.7 Median: 3	Mean: 2.8 Median: 3
	June 1, 2002 to August 28, 2005	Mean: 2.6 Median: 2	Mean: 3.0 Median: 3
PRESTO	December 4, 2000 to May 31, 2002	Mean: 2.8 Median: 3	Mean: 2.9 Median: 3
	June 1, 2002 to August 28, 2005	Mean: 2.8 Median: 3	Mean: 2.9 Median: 3

FDA Table 12: MRFs by Time from Study Start for Continuing and Discontinuing Rasagiline Subjects in TEMPO and PRESTO (Adapted from Sponsor Table 14 and Table 16, Appendix A, Ref. 1)

Study	Time Period	PD Duration in Continuation Cohort	PD Duration in Discontinuation Cohort
-------	-------------	------------------------------------	---------------------------------------

¹³ The Melanoma Risk Factors collected by Teva were: fair complexion, blue eyes, blond or red hair, history of severe childhood sunburn, family history of melanoma, personal history of melanoma, inability to tan, freckles, congenital mole, changing mole, immunosuppression and one or more large or irregular pigmented lesions (Teva NDA Submission, Integrated Summary of Safety, Appendix 18.3, pg. 30).

TEMPO	0-6 Months	Mean: 2.7 Median: 3	Mean: -- Median: --	
	0-12 Months	Mean: 2.7 Median: 3	Mean: -- Median: --	
	0-24 Months	Mean: 2.7 Median: 3	Mean: 1.5 Median: 2	
	0-36 Months	Mean: 2.7 Median: 3	Mean: 1.0 Median: 0	
	0-48 Months	Mean: 2.7 Median: 3	Mean: 3.3 Median: 3	
	0-60 Months	Mean: 2.7 Median: 2	Mean: 2.8 Median: 3	
	0-96 Months	Mean: 2.6 Median: 2	Mean: 3.0 Median: 3	
	PRESTO	0-6 Months	Mean: 2.8 Median: 3	Mean: 2.7 Median: 3
		0-12 Months	Mean: 2.8 Median: 3	Mean: 2.9 Median: 3
0-24 Months		Mean: 2.8 Median: 3	Mean: 2.9 Median: 3	
0-36 Months		Mean: 2.7 Median: 3	Mean: 2.9 Median: 3	
0-48 Months		Mean: 2.8 Median: 3	Mean: 2.9 Median: 3	
0-60 Months		Mean: 2.8 Median: 3	Mean: 2.9 Median: 3	

Levo-Dopa Treatment (TEMPO)

For the calendar time analysis (FDA Table 13), Teva stated that the proportion of TEMPO patients treated with levo-dopa (L-dopa) was similar for the two cohorts in the time periods before and after first dermatologic screening for 90% of patients.

For the time from study start analysis, (FDA Table 14), the sponsor noted that, as one would expect, there is an increase in L-dopa treatment over time in the Continuation Cohort.

Teva noted there was a pattern of increasing in L-dopa treatment over time in the patients who continued in the study. Teva asserted that this pattern is expected, because in TEMPO additional PD therapy was allowed only after the placebo-controlled phase was completed. Therefore, all patients started rasagiline treatment without L-dopa treatment, and subsequently there was an increase over time.

Teva believed that the comparison of L-dopa treatment between the Continuation and Discontinuation Cohorts is less reliable than for the other factors examined above,

because the exposure for discontinuing subjects was less than for continuing subjects (Ref. 1, pg. 16).

Reviewer comment: *In the preceding sentence, it is unclear whether Teva is referring to the exposure for the Discontinuation Cohort being less reliable, or the data collection being less complete (i.e. if a patient discontinued due to lack of efficacy, and after discontinuation started L-dopa, this would likely not be captured.) It seems that both factors would be contributory.*

FDA Table 13: L-Dopa Treatment by Calendar Time for Continuing and Discontinuing Rasagiline Subjects in TEMPO (Adapted from Sponsor Tables 21, Appendix A, Ref. 1)

Study	Time Period	% L-Dopa Treated Patients in Continuation Cohort	% L-Dopa Treated Patients in Discontinuation Cohort
TEMPO	Nov. 7, 1997 to May 31, 2002	44%	35%
	June 1, 2002 to August 28, 2005	72%	69%

FDA Table 14: L-Dopa by Time from Study Start for Continuing and Discontinuing Rasagiline Subjects in TEMPO (Adapted from Sponsor Table 22, Appendix A, Ref. 1)

Study	Time Period	% L-Dopa Treated Patients in Continuation Cohort	% L-Dopa Treated Patients in Discontinuation Cohort
TEMPO	0-6 Months	15%	31%
	0-12 Months	17%	32%
	0-24 Months	27%	32%
	0-36 Months	38%	34%
	0-48 Months	49%	34%
	0-60 Months	62%	37%
	0-96 Months	72%	42%

Reviewer comment: Although Teva stated that the percentage of subjects treated with L-dopa increased over time in the Continuation cohort, it also did so in the Discontinuation cohort. However, the proportion of the Discontinuation cohort using L-dopa was double that in the Continuation Cohort in the first six months and only increased slightly over time compared with the Continuation cohort. In addition, in the time from study start analysis, for some time strata the percent of subjects with L-dopa was greater in the Continuation cohort and for others the percent of subjects was less in the Continuation cohort. Therefore, it is not possible to clearly characterize either of the two cohorts as having an increased melanoma risk, as suggested by L-dopa treatment¹⁴.

3.1.2.3 Conclusions

Teva concluded that, overall, the various comparative analyses between continuing and discontinuing patients in TEMPO and PRESTO demonstrated no meaningful differences in age, gender, PD duration, melanoma risk factors or L-dopa treatment. Teva stated this was true for both methods of evaluating time: calendar time and time from study start. The sponsor believed these analyses rule out the hypothesis that the patients who discontinued had a higher risk for melanoma.

Reviewer comment: As noted in the reviewer comments in each section above, the Continuation and Discontinuation cohorts do have small differences with regard to the demographic and treatment factors examined. However, some of the differences would be associated with an increased risk in the Discontinuation cohort (age) and others would be associated with a decreased risk in the Discontinuation cohort (gender). Therefore, as noted by Teva, these analyses do not support the presence of a meaningfully elevated melanoma risk among discontinuing subjects. This is reassuring with respect to the melanoma incidence over time plot which prompted this comparison (see Section 2.5.3). If no increased risk of melanoma is observed in the discontinuing subjects compared to the continuing subjects (in other words, discontinuing subjects are not more susceptible to melanoma), then the fall in melanoma rates over time of rasagiline exposure cannot be attributed to loss to follow-up of higher risk patients who have discontinued. As noted by the sponsor, one would expect a carcinogen to cause increased rates with time, which is not seen with rasagiline.

3.2 Immediate/Delayed Exposure: Updated Data

3.2.1 FDA Question to Teva

“In the briefing packet, you noted that several programming errors affected some of the results previously provided (pg. 6). Please provide a version of Table 19 below using the corrected data. You should have already received this table as part of the shared FDA melanoma review, but it is also included below for your

¹⁴ L-dopa treatment has been associated with melanoma in published case reports and case series; L-dopa treatment is also a marker for more advanced disease.

convenience.”(Ref. 11)

FDA Table 15 (pg. 35): Number and Risk of Melanomas in the Immediate and Delayed Start Groups by Time Strata from Time of *First Study Dose (Placebo or Rasagiline)*

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 (0.8%)	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%)

3.2.2 Sponsor Response with Reviewer Comments

Reviewer comment: *Although Teva also supplied tables with data as of a August 2004 datalock, only the tables from the more recent datalock of August 2005 are presented in this review. The tables from August 2005 differed from the August 2004 tables in that four more melanomas had accumulated in the “>24 Months” time strata.*

Teva made several changes in the FDA assignment of melanoma cases to the time strata. The FDA reviewer used the time to diagnosis in the original NDA submission¹⁵ to assign cases, and following an e-mail request for clarification¹⁶, the sponsor explained that these times to diagnosis should be corrected. The changes in the case assignments to time strata made by Teva were:

1. For **Patient 246**, the time on rasagiline until diagnosis as stated in the Teva submissions was **1.33 years (16.0 months)** in the original ISS, and 1.55 years (18.6 months) in the January 2006 submission. Teva explained that the inconsistency stemmed from a three-month gap between the end of the TEMPO active phase and the start of the extension study, during which time the subject was not receiving the study drug. In the January 2006 submission, Teva included these three months off rasagiline in their determination of 18.6 months as the time from study drug start.

Reviewer comment: *Because the time the subject actually received rasagiline, as opposed to the total time from start of the study drug, is more biologically relevant to the potential relationship to melanoma development, the three-month*

¹⁵ The time to diagnosis used by the FDA reviewer were taken from the Integrated Summary of Safety in the original NDA submission, Appendix 18.3, Attachment 2.

¹⁶ E-mail communication from Teva representative Dennis Williams received March 27, 2006.

gap off rasagiline between the two study phases should not be included in the exposure calculation. The time of 1.33 years (16.0 months) should therefore be used as the rasagiline exposure time.

2. For **Patient 113**, the time to diagnosis in the original NDA (1.1 years, 13 months) was incorrect, and the time to diagnosis in the January 2006 submission (**0.93 years, 11 months**) was correct. Teva explained that the inconsistency arose from confusion over the time of the diagnostic biopsy (— , —) and the time of an additional excision — .
3. **Patient 613** was exposed to rasagiline for **0.51 years (6.1 months)** and was allocated by FDA reviewer to the 0-6 month strata. The correct case allocation is the 6-12 months strata.

Reviewer comment: *Based on the information provided by Teva and review of my original case assignments, I believe that the corrected case assignments for Patients #113 and #613 above are the appropriate ones for use in the analysis. The tables below assign these two cases to the correct time strata. In addition, in the table below I have included Patient #246 in what I consider to be the appropriate strata (12-18 months, as opposed to 18-24 months.)*

Table 16 below shows the changes in the original version of this table (shown in Section 3.2.1) from the correction of the programming error¹⁷, the re-assignment of three cases within the time strata and the ongoing time accumulation. Table 17 shows the table after these changes have been made.

**APPEARS THIS WAY
ON ORIGINAL**

¹⁷ Teva stated that the programming errors arose from mistakes in the SAS program, which affected both treatment allocation and dose assignment in the dose response analyses presented by the FDA in Tables 4-6, Ref. 10, based on data previously provided by Teva (Ref. 6, pg. 41).

FDA Table 16: Changes due to Corrections and Ongoing Exposure in Risk and Number of Melanomas in the Immediate and Delayed Start Groups from Time of First Study Dose

Cases Per Treatment Group	0-6 Months	6-12 Months	12-18 Months	18-24 Months	>24 Months
PRESTO Immediate	<u>3 (1%)^a</u> - 1 Case ^b 2 (0.6%)^c	<u>2 (0.6%)</u> +1 Case 3 (1.0%)	<u>1 (0.3%)</u> 1 (0.3%)	<u>0</u> 0	<u>0</u> 0
PRESTO Delayed	<u>0</u> 0	<u>0</u> +1 Case 1 (0.6%)	<u>1 (0.6%)</u> -1 Case 0	<u>0</u> 0	<u>0</u> 0
TEMPO Immediate	<u>1 (0.4%)</u> 1 (0.4%)	<u>0</u> +1 Case 1	<u>2 (0.7%)</u> - 1 Case 1 (0.4%)	<u>0</u> 0	<u>6 (2%)</u> +1 Case 7 (2.6%)
TEMPO Delayed	<u>0</u> 0	<u>0</u> 0	<u>0</u> 0	<u>0</u> 0	<u>1 (0.7%)</u> +1 Case 2 (1.4%)
Total Immediate	<u>3 (0.5%)</u> 3 (0.5%)	<u>2 (0.3%)</u> +2 Cases 4 (0.7%)	<u>3 (0.5%)</u> -1 Case 2 (0.4%)	<u>0</u> 0	<u>6 (1%)</u> +1 Case 7 (1.2%)
Total Delayed	<u>1 (0.3%)</u> -1 Case 0	<u>0</u> +1 Case 1 (0.3%)	<u>1 (0.3%)</u> -1 Case 0	<u>0</u> 0	<u>1 (0.3%)</u> +1 Case 2 (0.7%)

- The underlined values in the first line of the cell represent the value for that cell in the original version of the table from the FDA's Response to the Approvable Letter Review, dated July 27, 2005.
- The second line in the cell represents the change in case number (if any) from the original versions to the corrected version, presented in Table 17 of this review.
- The bolded values in the third line of the cell represent the value for that cell in the corrected version of the table, presented in Table 17 of this review.

Reviewer comment: As shown by the table above, a little more than half the cells were changed due to the corrections based on the re-assignment of the three cases, the correction of the programming error and the accumulation of additional exposure. However, the risk of melanoma in each time strata is relatively similar in the original and corrected versions of the table. Furthermore, the overall pattern of risk, with melanoma diagnosed earlier in PRESTO and later in TEMPO, is preserved in the corrected version of the table. This pattern between the trials is likely due to the timing of the beginning of active dermatologic screening with respect to the trial timeline, with TEMPO being well underway by the time the screening began. In both tables, the risk in the Immediate Start group is higher than in the Delayed Start group.

Table 17 below shows the corrected version of the table, with all the changes discussed above incorporated. It corresponds to the third, bolded row for each cell in Table 16 above.

FDA Table 17: Risk and Number of Melanomas in the Immediate and Delayed Start Groups from Time of First Study Dose, with Programming Error Corrected (August 2005 Datalock)(Adapted from Sponsor Table 2, Ref. 1, pg. 19)

Number of Melanomas Per Treatment Group	0 – 6 Months	6-12 Months	12-18 Months	18-24 Months	>24 Months
PRESTO Immediate	2 (0.6%)	3 (1%)	1 (0.3%)	0 (0%)	0 (0%)
PRESTO Delayed	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
TEMPO Immediate	1 (0.4%)	1 (0.4%)	1 (0.4%)	0 (0%)	7 (2.6%)
TEMPO Delayed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)
Total Immediate	3 (0.5%)	4 (0.7%)	2 (0.4%)	0 (0%)	7 (1.2%)
Total Delayed	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	2 (0.7%)

In addition to submitting Table 17 with the corrected data, Teva calculated incidence rates with 95% confidence intervals (CIs) for the Immediate versus Delayed Start cohorts across time strata. Teva noted that the 95% confidence intervals for all the treatment groups¹⁸ in all time strata overlap.

FDA Table 18: Melanomas per 1,000 Person-Years in the Immediate and Delayed Start Groups by Time Strata from First Study Dose (Adapted from Sponsor Table 4, Ref. 1, pg. 20)

**APPEARS THIS WAY
ON ORIGINAL**

¹⁸ The treatment groups are the PRESTO Immediate and PRESTO Delayed groups, the TEMPO Immediate and TEMPO delayed groups, and the Total Immediate and Total Delayed groups.

Number of Melanomas Per Treatment Group	0-6 Months	6-12 Months	12-18 Months	18-24 Months	>24 Months
Presto Immediate	13.9 (Obs=2, N=313, PY=143.6, 95% CI=1.6-50.3)	26.9 (Obs=3, N=263, PY=111.5, 95% CI=5.4-78.6)	11.6 (Obs=1, N=196, PY=86.5, 95% CI=0.2-64.3)	0 (Obs=0, N=160, PY=74.3, 95% CI=0-62.3)	0 (Obs=0, N=139, PY=176.1, 95% CI=0-26.4)
Presto Delayed	0 (Obs=0, N=159, PY=72.9, 95% CI=0-63.5)	17.4 (Obs=1, N=132, PY=57.5, 95% CI=0.2-96.8)	0 (Obs=0, N=95, PY=39.9, 95% CI=0-115.4)	0 (Obs=0, N=73, PY=34.5, 95% CI=0-133.2)	0 (Obs=0, N=63, PY=79.4, 95% CI=0-58.4)
Presto Immediate	7.8 (Obs=1, N=266, PY=127.5, 95% CI=0.1-43.6)	8.4 (Obs=1, N=248, PY=119.4, 95% CI=0.1-46.6)	0 (Obs=0, N=212, PY=95.3, 95% CI=0-48.7)	11 (Obs=1, N=186, PY=90.8, 95% CI=0.1-61.3)	11.3 (Obs=7, N=178, PY=621.3, 95% CI=4.5-23.2)
Presto Delayed	0 (Obs=0, N=138, PY=67.3, 95% CI=0-68.8)	0 (Obs=0, N=130, PY=61.8, 95% CI=0-74.8)	0 (Obs=0, N=111, PY=52.4, 95% CI=0-88.1)	0 (Obs=0, N=99, PY=48.5, 95% CI=0-95.1)	5.9 (Obs=2, N=94, PY=337, 95% CI=0.7-21.4)
Total Immediate	11.1 (Obs=3, N=579, PY=271.1, 95% CI=2.2-32.3)	17.3 (Obs=4, N=511, PY=230.9, 95% CI=4.7-44.4)	5.5 (Obs=1, N=408, PY=181.8, 95% CI=0.1-30.6)	6.1 (Obs=1, N=346, PY=165.1, 95% CI=0.1-33.7)	8.8 (Obs=7, N=317, PY=797.4, 95% CI=3.5-18.1)
Total Delayed	0 (Obs=0, N=297, PY=140.2, 95% CI=0-33.1)	8.4 (Obs=1, N=262, PY=119.3, 95% CI=0.1-46.6)	0 (Obs=0, N=206, PY=92.3, 9 5% CI=0-50.2)	0 (Obs=0, N=172, PY=83, 95% CI=0-55.8)	4.8 (Obs=2, N=157, PY=416.4, 95% CI=0.5-17.3)

Reviewer comment: In Teva’s table above, Patient #246 is included in the 18-24 Month time strata. As discussed on page 32 above, it is more appropriate to place it in the 12-18 Month time strata. This affects the rates for the TEMPO immediate row in both these time strata. (In the first column, the third and fourth cells from the top should be labeled “Tempo Immediate” and “Tempo Delayed.”)

The only pattern I observed in the table above was the higher rate of melanomas in the Immediate Start compared to the Delayed Start group. However, as noted by the sponsor, the confidence intervals for all cells overlap. There does not appear to be a consistent trend in melanoma rates across time strata. One can observe, however, that although the number of cases is highest in the “>24 months” strata, when adjusted for exposure the highest rates occur in the “6-12 Months” strata. Finally, the number of cases per cell, especially in the earlier time strata, is quite small. Due to all these factors, it is difficult to draw conclusions regarding the effect of immediate versus delayed start of rasagiline on melanoma development from this data.

3.3 Pre-Screening Melanoma Cases

3.3.1 FDA Question to Teva

“Regarding the number of melanoma cases which should be included in the pre-

screening melanoma rate calculation:

- a) The briefing packet noted that there were six melanomas (four in situ and two invasive) identified prior to initiation of mandatory dermatological screening (pg. 11). At the meeting there was discussion that the more appropriate case count is three melanomas. Assuming that you would exclude the advanced melanoma occurring two months after study initiation, which other melanoma cases do you believe should not be included among the six pre-screening cases (i.e., which other two cases occurred after the "Dear Investigator" letter and before screening began?)
- b) To clarify, were there melanoma awareness measures (the "Dear Investigator" letter along with the Investigator Brochure) prior to the initiation of screening? What were the approximate dates for these measures and the initiation of screening? Is there any evidence that the pre-screening melanoma awareness activities resulted in heightened melanoma detection?" (Ref. 11)

3.3.2 Sponsor Response with Reviewer Comments

Teva described the chronology of melanoma awareness activities as follows:

On December 8, 2000, a "Dear Investigator" letter describing the initial four melanomas (in Subjects TEMPO #113, #164, #246 and #009) was sent to all rasagiline investigators. Subsequently, on February 8, 2001, a melanoma assessment report was sent to all investigators, which contained (Ref. 1, pg. 22):

- Further details on the initial four melanomas
- An epidemiologic perspective on melanoma
- A review of melanoma in relation to Parkinson's disease, with a comparison of the rasagiline melanoma events to those in three other PD studies: ROADS, CALM-PD, and ELLDOPA
- An expert opinion on the four melanomas prepared by the _____
- A cover letter instructing all sites to modify their Informed Consent related to the risk of melanoma
- Instructions to have all active subjects sign a revised consent no later than their next visit

During that same month (February 2001), Teva revised the Investigator's Brochure with respect to melanoma.

On _____, two lesions were excised from Subject #064. The subsequent pathology report identified one lesion as melanoma in-situ (Ref. 1, pg. 23).

On April 5, 2001, all sites were sent another letter providing follow-up information for the fourth melanoma case (Subject #009).

On May 23, 2000, Subject #036 reported a lesion on his face and was encouraged to see a dermatologist. A biopsy on _____ revealed melanoma in-situ.

In addition to the melanoma-related correspondence described above, Teva noted that each investigator submitted an IND safety report and revised informed consent regarding melanoma risk to their IRB¹⁹. Teva emphasized that because investigators were frequently involved in multiple rasagiline trials concurrently, they would have received several copies of the previously described correspondence and submitted paperwork to several IRBs (Ref. 1, pg. 23).

Teva asserted that while the chronology of events does not constitute evidence of "heightened melanoma detection," it is reasonable to conclude that the extent and timing of these activities increased melanoma awareness among investigators and subjects. Consequently, Teva believes that Subjects #064 and #036 should not be included among the six pre-screening melanomas. As noted in a prior submission²⁰, Teva also believes that the case of advanced melanoma diagnosed two months after study initiation (Subject # 164) should be excluded. Therefore, Teva concluded that only three cases (Subjects #113, #246, #009) should be included in the pre-screening rate calculation (Ref. 1, pg. 23).

***Reviewer comment:** The decision to exclude cases based on confounding factors and or other case characteristics is a difficult one, as presumption of causality must be made for individual cases. For the rasagiline development program, the situation is further complicated by melanoma awareness activities leading to a detection bias. Previous review²¹ has documented that such a surveillance bias occurred, and the question here is which were the earliest cases impacted by increased melanoma awareness. The timing of the biopsies in Subjects #064 and #036 suggests that they may have been affected, and in the latter case the subject was apparently encouraged at one of his study visits to see a dermatologist. However, since such retroactive assumptions are not verifiable, the most conservative measure is to retain these cases, with awareness that their inclusion among the pre-screening cases may be unwarranted. To address the potential for their incorrect inclusion, the rate of pre-screening melanomas within the rasagiline development program should additionally be calculated with these cases excluded, as presented below:*

¹⁹ IRB=Institutional Review Board

²⁰ Meeting briefing packet for the FDA/Teva meeting on December 7, 2005.

²¹ NDA 21-641 (Rasagiline). Clinical Review: NDA Primary Safety Review. Prepared by M. Lisa Jones, MD, MPH. Dated July 5, 2004.

FDA Table 19: Rate of Pre-Screening Melanomas within the Rasagiline Development Program

Number of Pre-Screening Melanomas	Rate Per 1000 PYs*
Six Melanomas	5.8
Five Melanomas	4.8
Four Melanomas	3.9
Three Melanomas	2.9

* The melanoma rate per person-year exposure was calculated using 1034 person-years as the approximate person-time in the total rasagiline exposure until melanoma screening commenced (October to December 2003), based on exposure estimates supplied by Teva.

In prior reviews²², the rate of melanomas in the rasagiline development program has been compared to that of other PD development programs. To address the surveillance bias from active melanoma screenings within the rasagiline development program, the comparison was restricted to only those melanomas diagnosed prior to the screening program. The table below shows this comparison using three to six pre-screening melanomas in the rasagiline melanoma rate calculation. Of note, even when the number of pre-screening melanomas is limited to three, the rate of melanomas in the rasagiline development program exceeds that of the other PD development programs. However, the 95% confidence intervals generally overlap (see FDA Table 20 below).

FDA Table 20: Melanomas in the Rasagiline Development Program Diagnosed Prior to Dermatologic Screening Compared to Melanomas in Other PD Therapy Development Programs

PD Therapy Development Program: Principle Drug*	# of Melanomas	Total PYs**	Incidence Density per 1000 PYs	95% Confidence Intervals ²³
Pergolide	0	930	NA	NA
Pramipexole	11	6909	1.6	(0.8, 2.8)
Ropinirole	1	3377	0.3	(0.02, 1.5)
Entacapone	0	2486	NA	NA
Tolcapone	4	3200	1.3	(0.4, 3.0)
Rasagiline	6	1034	5.8	(2.4, 12.1)
	5		4.8	(1.8, 10.7)
	4		3.9	(1.2, 9.3)
	3		2.9	(0.7, 7.9)

²² NDA 021-641 (Rasagiline). Primary Safety Review and Amendment. Prepared by Dr. M. Lisa Jones.

²³ Confidence intervals on rates calculated with the Mid-P exact test using calculator at

<http://openepi.com/Menu/OpenEpiMenu.htm>

Clinical Review

M. Lisa Jones, MD, MPH

NDA 21-641

Rasagiline (Azilect®)

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

** Approximate person-years in the rasagiline development program until the beginning of melanoma screening (October to December 2001).

3.4 Dose-Response: Cumulative Dose

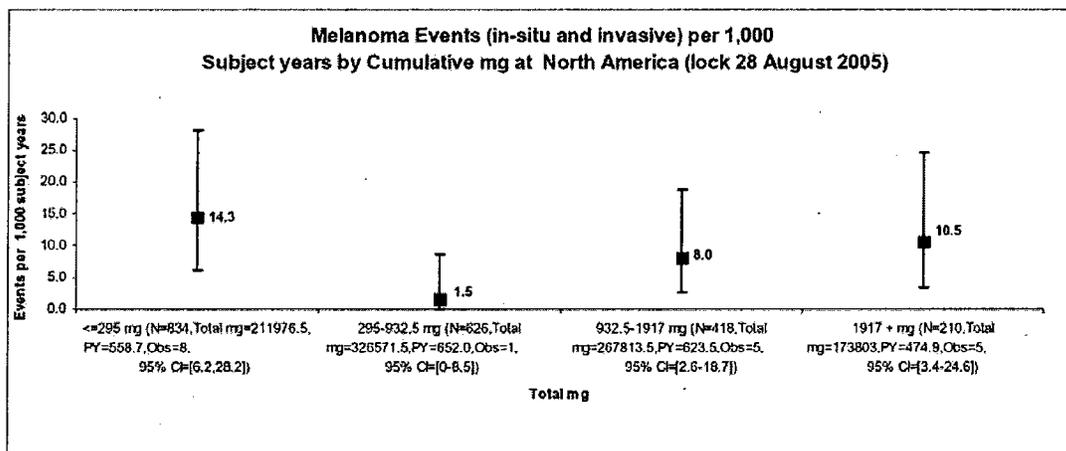
3.4.1 FDA Question to Teva

“At the meeting, a dose-response analysis using cumulative dose was shown. Please provide us with the results of this analysis (including confidence intervals for the point estimates).”(Ref.11)

3.4.2 Sponsor Response with Reviewer Comments

Teva provided a dose-response analysis using cumulative dose at time of melanoma diagnosis, shown below (Table 21). The sponsor clarified that each patient contributed to each dose interval until censored, and that the figure reflects the latest database lock of August 28, 2005 (Ref. 1, pg. 24).

FDA Table 21: North American Melanomas (Invasive and In Situ) per 1000 PYs by Cumulative Dose (Taken from Sponsor Figure 19, Melanoma Response, pg. 24)



Reviewer comment: The rate of melanoma per 1,000 PYs by cumulative dose in the table above does not demonstrate a clear dose-response pattern. In fact, although the confidence intervals of all the dose strata overlap, the highest point estimate is observed in the lowest exposure strata (<295 mg). However, if one excludes the lowest strata under the presumption that pre-existing melanomas were diagnosed in this time period,

there is a slight dose response relationship, although not a significant one as evidenced by the overlapping confidence intervals.

Teva did not specify how they chose their cut-off points of the exposure strata (for instance, if these strata divided cumulative exposure into quartiles.)

3.5 Discontinuation Due to Patient/Physician Decision

3.5.1 FDA Question

“An additional note regarding the safety update:

Within the section on patient discontinuation, for patients who discontinued for reasons of “physician decision” or “patient decision,” please examine the case report form and any other available information for underlying reasons for the discontinuation (and include that information, where identified).”(Ref. 11)

3.5.2 Sponsor Response with Reviewer Comments

Teva stated that additional information on discontinuations due to “physician” or “patient decision” was obtained from case report forms (CRFs) and communications with the study sites, with a data lock of February 16, 2005. Teva specified that the discontinuations described in the sections below related to the patient’s “medical condition,” i.e., the possible influence of an AE. The sponsor also provided information²⁴ on discontinuations due to the need for a disallowed medication, melanoma-related issues, unsatisfactory response/worsening of PD or protocol violation, but these are not specifically discussed in this section (Ref. 2, pg. 32).

Teva noted that all discontinuation narratives for the placebo-controlled studies, regardless of discontinuation reason, were included in the NDA submission.

***Reviewer comment:** Although all discontinuation narratives were included in the NDA, it is clearly important that any AEs leading to the discontinuation be identified as and counted within the most appropriate AE category.*

Monotherapy Study TEMPO

In the monotherapy study TVP-1012/232 TEMPO (or Cohort 1²⁵, as per the sponsor’s NDA analysis cohorts), Teva reported that four discontinuations “due to patient’s request” were identified as possibly AE-related upon further evaluation:

²⁴ Integrated Summary of Safety (ISS), Ref. 2, Appendix 7.5.1 and 7.5.2

²⁵ In addition to the larger pivotal trial TEMPO, Teva’s Cohort 1 also contained 56 patients from a smaller monotherapy trial TVP-1012/231.

Reviewer comment: Among the four discontinuations referred to immediately above, I only include details on the two rasagiline-treated subjects. I have not included details on the other two subjects (TVP-1012/232 #213 and TVP-1012/232 #309), as both were in the placebo group.

1. **TVP-1012/232 (PC²⁶ Phase) #345 (1 mg):** This 63-year-old man requested to discontinue due to depression, which was reported as an AE one month prior to discontinuation.
2. **TVP-1012/232 (PC Phase) #424 (2 mg):** This 62-year-old woman requested to withdraw due to the AE of “toxic metabolic reaction due to the combination of medications.” The event occurred following hospitalization for worsening depression, approximately a month after starting rasagiline. The patient had a ten-year history of bipolar affective disorder, and also suffered chronic neck pain. The investigator considered the toxic metabolic reaction an interaction of all the patient’s medications (valproic acid, nortriptyline, estrogen, trazodone, naproxen, lithium and aspirin). Action of “dose stopped” was recorded on the CRF for toxic metabolic reaction (coded as drug interaction), as well as confusion, dizziness, somnolence and dysarthria occurring at the same time.

Reviewer comment: The information on this subject in Appendix 7.5.1. of the ISS did not comment on how the diagnosis of toxic drug interaction was reached.

Teva stated that inclusion of the four cases above resulted in an increase in early discontinuations due to AE from 4.0% to 4.7% (1 mg), 1.4% to 2.1% (2 mg), and 0.7% to 2.0% (placebo). The sponsor reported that depression was the only new AE added to the 1 mg dose, although it did not fulfill the criterion for “adverse events leading to discontinuation of more than one rasagiline-treated patient”(Ref. 2, pg. 34).

Adjunct Therapy (PRESTO)

In the levo-dopa adjunct study TVP-1012/133 (PRESTO), Teva identified two discontinuations (one in the rasagiline group and one placebo) initially classified as “due to patient’s request” that were possibly AE-related:

1. **TVP-1012/133 #453 (0.5 mg):** On the day of the first rasagiline dose, this 64-year-old man fell due to loss of balance. After about six weeks on drug, he complained of low blood pressure and drowsiness, followed four weeks later by loss of appetite. A weight loss of eight kilos was documented. The narrative stated that the subject withdrew consent because he did not experience any benefit and felt generally unwell, which he attributed to rasagiline. Action taken of “dose stopped” was recorded on the CRF for hypotension (105/67 supine and 75/60 standing at termination visit), loss of appetite (coded as anorexia) and somnolence.

²⁶ PC=Placebo-Controlled
Clinical Review
M. Lisa Jones, MD, MPH
NDA 21-641
Rasagiline (Azilect ®)

Teva stated that the addition of the above AEs resulted in an increase in discontinuations due to AE in PRESTO from 8.5% to 9.1% (0.5 mg), from 5.0% to 5.7% (placebo), with the 1 mg group remaining unchanged at 6.7%. Somnolence was the only new AE fulfilling the criterion of “adverse events leading to discontinuation of more than one rasagiline-treated patient.”

Reviewer comment: Teva did not specifically discuss discontinuations in the non-North American adjunct study LARGO. However, two subjects from the LARGO open-label extension are included in the Cohort 9 section below.

Cohort 9: All PD Patients Ever Exposed To Rasagiline

Teva stated that, overall, 297 rasagiline-treated patients discontinued due to various “other” reasons. The sponsor identified eight possibly AE-related cases, previously coded as “patient/physician request,” in addition to the six discussed above (Ref. 2, pg. 35).

1. **TVP-1012/123 #30301 (delayed²⁷ 1 mg).** This 70-year-old man reported declining mobility. He also experienced polyuria, polydipsia and elevated blood glucose, which were ultimately diagnosed as diabetes mellitus. He wished to discontinue due to the worsening of his overall condition.
2. **TVP-1012/123 #41606 (delayed¹² 1 mg).** This 65-year-old woman requested to discontinue due to constipation, dysthymia (coded as depression) and dizziness. Teva stated that the subject characterized these as long-standing.
3. **TVP-1012/135 #1 (1 mg).** This 62-year-old woman developed a rash two weeks after entering the extension study, and withdrew a week later due to the AE of rash. The investigator deemed the rash as unlikely related to the study drug and the reason for discontinuation was recorded as “withdrew consent.”
4. **TVP-1012/135 #85 (1 mg).** This 66-year-old man was hospitalized twice within two months for radiculopathy and weight loss. Although the study drug was not interrupted during the hospitalization for weight loss, the patient later decided to discontinue the study.
5. **TVP-1012/135OL #524 (1 mg).** This 75-year-old man experienced increased falls which, as per the subject, were not related to orthostatic dizziness. The study drug dose was decreased to 0.5 mg daily. The subject self-discontinued the study medication four days later, however, following another fall. The subject subsequently notified the site of his decision to discontinue the study.

²⁷ “Delayed” means that the subject received placebo in the preceding study (TVP-1012/122).

6. **TVP-1012/233 #155 (1 mg).** This 39-year-old man was titrating ropinirole when he developed paranoia, loss of memory and hallucinations. He was instructed to stop taking ropinirole and his psychiatrist hospitalized him due to psychosis. On the day of admission, the patient permanently stopped the study drug without consulting the investigator. The investigator discontinued the patient due to non-compliance.
7. **TVP-1012/233 #319 (2 mg).** This 68-year-old woman entered the study with hypertension treated with multiple medications. Hypertension was recorded as an AE on the day of termination. The patient and investigator decided to discontinue the study to better focus on her blood pressure control.
8. **TVP-1012/233 # 580 (1 mg).** This 68-year-old man with a history of hypertension discontinued due to poor blood pressure control, as recommended by his cardiologist.

Teva stated that addition of these 11²⁸ rasagiline-treated patients increased the overall risk of AEs from 12.6% to 13.4%. Teva noted that only three of the newly attributed AEs (drug interaction, diabetes mellitus and dysarthria) had not been “already noted for this cohort as leading to early termination.” The sponsor provided the table below summarizing the newly-attributed AEs from their re-analysis of discontinuations due to “patient/physician decision”(Ref. 2, pg. 36).

FDA Table 22: Additional AEs leading to Early Discontinuation Based on Re-Evaluation of Discontinuation Reasons Other than “Due to AE” (Adapted from Sponsor Table 16, Ref. 2, pg. 36)

**APPEARS THIS WAY
ON ORIGINAL**

²⁸ The eleven rasagiline-treated patients were the eight in the Cohort 9 section, plus the three from the monotherapy and adjunctive therapy sections above.

Adverse Event that Led to Discontinuation	N=1361	
	Final ISS	Patients Added
	No. of Patients	No. of Patients
Accidental Injury	3	1
<i>Drug Interaction</i>	0	1
Fall	7	1
Hypertension	10	2
Hypotension	1	1
Anorexia	1	1
Constipation	2	1
<i>Diabetes Mellitus</i>	0	1
Weight Loss	3	1
Confusion	3	1
Depression	6	2
Dizziness	9	2
<i>Dysarthria</i>	0	1
Psychosis	8	1
Somnolence	2	2
Rash	5	1

Reviewer comment: In the table above, the column titled "Final ISS" refers to the number in the January 2006 safety update, without the newly attributed AEs in this section added (the new AEs are counted in the second column "Patients Added." Teva should have included the new cases within a "final" count of AEs.

The sponsor review, at the request of the FDA, of discontinuations due to "physician/patient decision" resulted in the capture of 11 additional AEs in the rasagiline treatment group, including some in categories that have been of particular concern, such as falls. However, as the additional AEs were relatively few in number and in varied categories, there were no substantial changes to rasagiline's overall AE profile.

4. PHASE IV STUDY PROTOCOL

4.1 Overview

Teva described its proposed Phase IV melanoma study as a multi-center, double-blind, placebo-controlled, "add-on" treatment study. The estimated total enrollment is 5200

subjects (drawn from the United States), and the study will run for 36 months (Ref. 3, pg. 7).

4.2 Subjects

Study recruitment will occur at 150 study sites throughout the United States. Subjects will be assessed for eligibility at a screening visit conducted up to four weeks prior to baseline. Inclusion criteria are a confirmed diagnosis of PD and ability to give informed consent. Exclusion criteria are:

1. Significant medical or surgical conditions that preclude safe study participation.
2. Prior history of melanoma, diagnosis of melanoma during the screening dermatology examination or refusal of biopsy of suspicious dermatologic lesions found during the baseline screening.
3. Previous exposure to rasagiline.
4. Use of selegiline within the two months prior to baseline.
5. Use of sympathomimetics (including over-the-counter remedies [nasal or oral]), dextromethorphan, pethidine or St. John's Wort within the seven days prior to baseline.
6. Use of antidepressants, including selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants (except: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily, paroxetine ≤ 30 mg/daily, escitalopram ≤ 10 mg/daily) within 42 days prior to baseline.
7. Use of MAO inhibitors, reserpine and methyl dopa within the three months prior to baseline, or treatment with an anti-emetic or antipsychotic medication with central dopamine antagonist activity (except quetiapine) within the six months prior to baseline.

Reviewer comment: *It is unclear why an exception was made for quetiapine in the exclusion criteria above.*

8. Women of childbearing potential without a negative pregnancy test.
9. Use of any experimental medications within 60 days prior to baseline.

Reviewer comment: *Exclusion of persons with a history of melanoma may reduce the number of melanomas occurring within the Phase IV study. Because a history of melanoma was not an exclusion criteria during initial recruiting for the pivotal trials of the rasagiline development program, the rate of melanomas in the proposed Phase IV study may be lower than in the pivotal trials. Teva should take this into account during their calculations of the number of subjects needed for an adequately powered study, as they used the melanoma rate in the pivotal trials to estimate the melanoma rate in the Phase IV study.*

4.3 Study Visits

Study participation will consist of a screening visit (-4 weeks), a baseline visit (0 week), followed by visits every six months until 36 months (Ref. 3, pg. 28).

4.4 Melanoma Screening and Diagnosis

Teva stated that subjects will undergo dermatologic examinations at screening and thereafter at the 6th month, 12th month, 24th month and 36th month visits. Examinations will be conducted by certified dermatologists. A biopsy will be performed on any suspicious lesion, and slides of all biopsy specimens will be evaluated by a central dermatopathologic facility. Subjects who are diagnosed with melanoma during the study will immediately terminate the study (Ref. 3, pg. 32).

4.5 Sample Size

Teva calculated that a total of 4400 subjects treated for three years will provide a power level of approximately 80% to detect non-inferiority between the rasagiline and placebo treatment arms in the incidence rate of melanoma. This is based on the assumption of an exponential distribution of time to melanoma, an incidence rate of four events per 1000 PYs in each treatment arm (as occurred in the pivotal trials) and an upper limit of the one-sided 95% confidence interval less than two (one-sided alpha level of 5%) for the risk ratio of melanoma in the rasagiline arm compared to the placebo arm.

Reviewer comment: As noted in Section 4.2 above, Teva should take into consideration that the rate of melanomas in the pivotal trials, which did not exclude persons with a history of melanoma during the initial recruiting, may be higher than in the Phase IV study, which will exclude persons with a history of melanomas.

Teva noted that an additional 800 patients will be needed to obtain the required total exposure in the study if one factors in a drop-out rate of 30%. Therefore, the total number of patients needed is approximately 5200. The sponsor reported that a reassessment of the melanoma incidence rate and sample size will be conducted during the study based on the blinded study data (Ref. 3, pg 41).

4.6 Treatment Protocol

Eligible subjects will be randomized on a one:one basis to one of two treatment groups:

1. 1 mg/day rasagiline
2. Placebo

Teva noted that because this is an “add-on” study, the use of all other anti-PD therapies (except selegiline) will be permitted, in addition to the study treatments. All anti-PD

therapies will be used as instructed by drug labeling and according to established medical practice. Subjects should continue to visit their regular general practitioner for treatment of their PD (Ref. 3, pg. 21).

4.7 Statistical Methods

Teva stated that the non-inferiority analysis for rasagiline and placebo with regards to the rate of melanoma will consist of a Poisson Regression. The model will include study center as well as PD and demographic characteristics (e.g. age, gender, PD duration, levodopa treatment at baseline, major melanoma risk factors²⁹)(Ref. 3, pg. 43).

5. SAFETY UPDATE

5.1 Adverse Events

5.1.1 Exposure and Overview

Teva noted that the same version of the COSTART system was used to code adverse events throughout the rasagiline development program. The sponsor also stated that varying AE terms between studies were unified for this safety summary.

Teva stated that the current Cohort 9 (all PD patients exposed to rasagiline) contains 1361 patients as of the CRF database lock, representing 2646 PYs of rasagiline exposure. Exposure per individual patient varied from one day to 8.7 years. The sponsor stated that AEs were reported by 86.3% of the Cohort 9 patients. Teva reported that exposure to rasagiline for the cohort increased by 12% compared to the previous safety report (Ref. 2, pg. 16).

5.1.2 Changes from Previous Safety Summary

Teva stated that the time-adjusted frequencies of AEs *by body system* in this update was similar to the previous safety report, including for cardiovascular AEs (previous safety update 36.8 reports/100 PYs and current update 37.6 reports/100 PYs). Teva attributed a slight increase in the time-adjusted frequency of AEs for Skin and Appendages (previous safety update 35.6 reports/100 PYs and current update 37.2 reports) to the proactive dermatologic screening uncovering a variety of skin lesions.

Teva reported that one new case of melanoma occurred (TVP/233 #616), which had already been included among the melanomas in the December 7th, 2005 meeting briefing packet (Ref. 2, pg. 17).

²⁹ Teva did not elaborate on how melanoma risk factors would be scored in the study analysis. However, in past submissions, Teva has used the total number of risk factors, with each weighted equally, to determine melanoma risk factor scores.

Reviewer comment: As dermatologic screening has been ongoing in the rasagiline development program since the initial NDA submission, it is unclear why this screening would lead to an increase in Skin and Appendage AEs compared to the prior update. The comparison to prior safety reports is also confounded by aging.

The table below shows the time-adjusted frequency of individual AEs by descending order of the difference between the current update and the previous update. Teva noted that the largest difference between the previous ISS and this update is seen for accidental injury (15 versus 13.8 reports/100 patient years)(Ref. 2, pg. 17).

FDA Table 23: Time-Adjusted Frequency of Adverse Events by COSTART Term and Descending Order of the Difference* of 'Final' Update vs. 'Pre-Approval' Update in Cohort 9 (Adapted from Sponsor Table 10, Ref. 2, pg. 17)

Final Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	No. of Reports Per 100 Patient Years (Revised Dictionary)		
	Final Update Rasagiline (N=1361)	Pre-Approval Update Rasagiline (N=1361)	Difference
ACCIDENTAL INJURY	15.0	13.8	1.2
FALL	13.6	12.8	0.8
PAIN	11.4	10.8	0.6
URINARY TRACT INFECTION	7.5	6.9	0.6
SLEEP DISORDER	10.2	9.7	0.5
HALLUCINATIONS	6.1	5.6	0.5
SKIN BENIGN NEOPLASM	6.0	5.5	0.5
SKIN CARCINOMA	8.0	7.4	0.5
PERIPHERAL EDEMA	8.8	8.4	0.4
BACK PAIN	10.4	10.1	0.4
CONFUSION	2.6	2.2	0.4
SKIN DISORDER	6.2	5.8	0.4

*Twelve most frequent AEs in the final database by the difference in time-adjusted frequency of Final vs. 'Pre-Approval' update

Teva interpreted the small differences in time-adjusted frequency of AEs between this update and the previous report as suggestive of no new rasagiline-related AEs having developed over time.

5.1.3 Common AEs

Teva stated that when grouped by body system, the highest number of reports per 100 PYs occurred in the Body as a Whole category (117/100PYs), followed by the nervous system (100/100 PYs), the digestive system (58/100 PYs), the cardiovascular system (38/100 PYs), the Skin and Appendages (37/100 PYs) and the urogenital system (28/100 PYs)(Ref. 2, pg. 17).

When ranked in descending order by time-adjusted frequency, Teva stated that the most frequent AEs included accidental injury (15/100 PYs), cold (13.6/100 PYs), fall (13.6/100 PYs), dizziness (12.7/100 PYs), headache (12.6/100 PYs), arthralgia (11.7/100

PYs), pain (11.4/100 PYs), nausea (11.0/100 PYs), back pain (10.4/100 PYs) and sleep disorder (10.2/100 PYs). Teva noted that accidental injury, infection (a part of which became the AE “cold” in the revised dictionary³⁰), headache, dizziness and pain were among the most frequently reported AEs in the placebo groups, as well as the rasagiline-treated groups, within the original ISS (Ref. 2, pg. 18).

5.1.4 Cardiovascular Events

Teva stated there were no prominent differences in cardiovascular AEs in the current safety update as compared to the previous report. Six new cardiovascular SAEs were reported in the CRF database for this cohort, which included:

- Chest pain and palpitations with negative cardiac workup (TVP-1012/233 #184)
- Peripheral vascular disorder (TVP-1012/135 #582)
- Post-operative deep vein thrombosis (TVP-1012/233 #53)
- Three other reports of lower extremity deep vein thrombosis (two reports in #173 and one report in #608)
- Observation for possible post-liver biopsy bleeding, coded as “hemorrhage” (TVP-1012/233 #59)

Reviewer comment: *Teva noted that although the event above was coded as hemorrhage, no hemorrhage actually occurred during the hospitalization (In other words, the hospitalization was for a cautionary observation of potential hemorrhage.).*

Additional cardiovascular/cerebrovascular AEs included:

- Two transient ischemic attacks (TVP-1012/233 #151 and TVP-1012/233 #428)
- Two angina/cardiac ischemic events (TVP-1012/135 #433 and TVP-1012/135 #276)

Reviewer comment: *The rate of myocardial ischemic events in Cohort 9 was 2.9 cases/100 PYs, unchanged from the prior safety report (Ref. 2, pg. 20)*

5.1.5 Neuropsychiatric Adverse Events

5.1.5.1 Psychosis

Teva asserted that about 20% of PD patients receiving dopaminergic agents long term will develop psychosis, and that this most commonly occurs in patients with cognitive impairment. Teva noted that psychosis was reported in the previous safety update and in this report with incidence of 0.7% versus 0.9%, and time-adjusted frequency of 0.6 versus 0.7 reports/100 PYs, respectively. The increase was accounted for by SAES in

³⁰ The revised dictionary refers to changes in AE coding requested by the FDA, such as creation of a new category for falls.

two patients. One (TVP-1012/135 #665) was addressed in the previous safety update. The other (TVP-1012/135 #485) was a 75-year-old man with a history of depression, insomnia and hallucinations treated with LD/CD, amantadine, entacapone, ropinirole, sertraline, donepezil and zolpidem. He developed psychosis, beginning the day after a hospitalization for hip fracture. After adjustment of his medications and addition of lorazepam and ziprasidone, he continued to receive the study drug (Ref. 2, pg. 21).

5.1.5.2 Agitation

Teva stated no new AEs of agitation were reported.

5.1.5.3 Paranoid Reaction or Delusions

Teva stated that no new *serious* AEs of paranoid reaction or delusions were reported. One patient (TVP-1012/135 # 129) reported an AE of paranoid reaction with memory loss, confusion and hallucinations, which resolved without change in the study drug. Another subject (TVP-1012/135 #329) reported delusions which resolved without change in the study drug. A third subject (TVP-1012/135 #482) developed moderate delusions with increased hallucinations (Ref. 2, pg. 21).

5.2 Deaths

From August 1, 2004 (the cut-off date for death reporting in the previous safety update) until December 31, 2005, eleven additional deaths in rasagiline-treated subjects occurred in the rasagiline development program: ten in the ongoing, open-label studies and one in a compassionate use program. Details of these eleven deaths are provided below (Ref. 2, pg. 22).

1. **TVP-1012/233 (TEMPO) #428 (5.8 years rasagiline, 2 mg then 1 mg/day³¹):** This 85-year-old woman was diagnosed with gastric carcinoma and died a short time later.
2. **TVP-1012/233 (TEMPO) #440 (6.5 years rasagiline, 1 mg/day):** This 73-year-old man with a remote history of asbestos exposure was diagnosed with mesothelioma. He died about six weeks later.
3. **TVP-1012/233 (TEMPO) #5 (6.0 years rasagiline, 2 mg then 1 mg/day³²):** This 65-year-old man with a history of hypertension, diabetes mellitus, hypercholesterolemia, lower extremity edema, increased ferritin levels and ECG abnormalities (questionable old inferior/anterior myocardial infarct) was found cold and pulseless in bed. Emergency services observed ventricular fibrillation

³¹ This patient was initially treated with rasagiline 2 mg/day (for about 9 months) followed by rasagiline 1 mg/day.

³² This patient was treated with rasagiline 2 mg/day for about one year, followed by rasagiline 1 mg/day.

which deteriorated into asystole and death. No autopsy was allowed and the cause of death was presumed to be myocardial infarction. His concomitant medications were pramipexole, bensmexol hydrochloride, glibenclamide, gemfibrosil, furosemide and lisinopril.

4. **TVP-1012/233 (TEMPO) #148 (6.4 years rasagiline, 2 mg then 1 mg/day³³):**
This 78-year-old man with a history of myocardial infarction, hypertension, arrhythmia and angina pectoris and diabetes mellitus was hospitalized for myocardial infarction during the core study. On _____ he was hospitalized due to disorientation, which resolved, and he was discharged to a rehabilitation facility. Since the patient could not be reevaluated in the clinic, new study drug could not be dispensed and the last dose was given on _____. Two weeks later, the patient was hospitalized with pneumonia. He refused a feeding tube and died of cardiac arrest on _____.
5. **TVP-1012/233 (TEMPO) #173 (6.7 years rasagiline, 2 mg then 1 mg/day³⁴):**
This 78 year-old-man entered the study with a history of transurethral prostatectomy, hypertension, nephrolithiasis, hypothyroidism, basal and squamous cell skin carcinoma, vitreous detachment, hyperglycemia, hematuria and a heart murmur. His concomitant medications were levodopa, carbidopa, sulconazole nitrate and esomeprazole magnesium. In _____ he was treated for left leg deep vein thrombosis. On _____, he was evaluated for confusion. His INR was 2.9. Warfarin was stopped and an MRI was unchanged compared to a prior study in 2003. On _____ he was seen by his internist for chest pressure, with ECG showing ST-T wave changes and PVC's. An echocardiogram was reported as not clinically significant and he was sent home with a Holter monitor. The next day, he was found unresponsive by his wife after lying down to rest. The Holter monitor showed pauses, subsequent ventricular fibrillation and asystole. An autopsy was not performed.
6. **TVP-1012/233 (TEMPO) #296 (5.5 years rasagiline, 2 mg then 1 mg/day³⁵):**
This 81-year-old man with a history of hypertension, arthritis, depression and difficulty swallowing with secondary weight loss was hospitalized for a cerebrovascular accident. Study medication was discontinued and he was transferred to a nursing home where he died shortly thereafter. The cause of death on the death certificate was CVA due to cerebrovascular disease. His concomitant medications were levodopa, carbidopa, ropinirole hydrochloride, amlodipine besylate and aspirin.

³³ This patient was treated with rasagiline 2 mg/day for about nine months, followed by rasagiline 1 mg/day.

³⁴ This patient was treated with rasagiline 2 mg/day for about seventeen months, followed by rasagiline 1 mg/day.

³⁵ This patient was treated with rasagiline 2 mg/day for about four months, followed by rasagiline 1 mg/day.

7. **TVP-1012/233 (TEMPO) #556 (5.9 years rasagiline, 2 mg then 1 mg/day³⁶):** This 85-year-old man with a history of asthma, hypertension, coronary artery bypass surgery, arrhythmia and heavy smoking was hospitalized in _____ for exacerbation of chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and pneumonia. He was treated with multiple cardiac drugs, diuretics, bronchodilators and inhaled/systemic steroids. Moderately severe aortic stenosis was diagnosed by echocardiogram. On _____, he had two generalized seizures and was found to have multiple metabolic abnormalities, including hyponatremia, hypokalemia and hypocalcemia. He was stabilized and discharged on _____. On _____ he became unresponsive with ventricular fibrillation noted during a resuscitation effort, which was unsuccessful.
8. **TVP-1012/135 (PRESTO) #346 (4.0 years rasagiline, 0.5 mg/day):** This 82-year-old man experienced a severe left intracerebral artery CVA³⁷ and died three days later. The patient had also been diagnosed with left lower lobe atelectasis or pneumonia.
9. **TVP-1012/135 (PRESTO) #439 (3.9 years rasagiline, 1 mg/day):** This 82-year-old woman with hypertension, hypercholesterolemia, cardiomegaly, ventricular hypertrophy and peripheral edema was hospitalized with chest pain. Her symptoms worsened and she died of a myocardial infarction later that day.
10. **TVP-1012/135 (PRESTO) #617 (3.3 years rasagiline, 1 mg/day):** This 71-year-old woman died about a month after being diagnosed with undifferentiated lung cancer.
11. **TVP-1012/Compassionate Use #70802 (2.4 years rasagiline³⁸, 1 mg):** An 84-year-old man with a history of atrial fibrillation died of pneumonia.

Teva reported that during the *entire* rasagiline clinical program (data accumulated until December 31, 2005), a total of 45 patients died: 34 rasagiline-treated patients [33 PD patients and one Alzheimer's disease patient], five placebo-treated PD patients and six entacapone-treated PD patients. The estimated³⁹ overall exposure until December 31, 2005 is 3077 patient-years (PYs). The overall (monotherapy and adjunct therapy combined) death rate in the rasagiline clinical trials is 9.7 cases per 1000 PYs of rasagiline use (30 cases/3077 PYs). Teva noted that this rate is similar to the overall rate reported for patients in the rasagiline treatment group during the placebo-controlled

³⁶ This patient was treated with rasagiline 2 mg/day for about seven months, followed by rasagiline 1 mg/day.

³⁷ CVA=Cerebrovascular Accident

³⁸ Duration of rasagiline treatment was 2.4 years assuming complete compliance while participating in the compassionate use program.

³⁹ Teva stated that this estimation is based on the August 2005 datalock.

phases of the trials (11.4 cases per 1000 PYs) and lower than the rate in placebo treatment groups (18.8 cases per 1000 PYs)(Ref. 2, pg. 24).

***Reviewer comment:** Upon reviewing the death narratives above as well as in the NDA and 120-Day summaries of safety, I observe no unusual pattern of deaths in rasagiline-treated patients. The causes of death are essentially those expected within an elderly population. More importantly, as noted in immediately above, the death rate in the rasagiline treatment group during the placebo-controlled portion of the trials was less than in the placebo treatment group.*

5.3 Serious Adverse Events (SAEs)

Teva stated that the CRF database cut-off date for this update was February 16, 2005. The sponsor reported that SAEs occurred in 25.9% of all rasagiline-treated patients. Of all the AEs reported, 6.7% (859/12,730) were SAEs. Time-adjusted frequency of SAEs in the updated CRF database was 32.5 reports/100 PYs, comparable to that of the previous safety report (29.5 reports/100 PYs) (Ref. 2, pg. 25).

5.3.1 Changes from Previous Safety Report

Teva maintained that in the majority of cases, SAEs by body system remained stable in time-adjusted frequency compared to the previous safety update. Exceptions were an increase in the time-adjusted frequency for body as whole (most prominently for accidental injury, with 2.2 events/100 PYs in the current update compared to 1.7/100 PYs in the prior update), but otherwise the differences were minor. The sponsor asserted that SAEs such as accidental injury, extrapyramidal syndrome, fall, hernia and prostatic carcinoma may be expected in a PD population with a large geriatric component (Ref. 2, pg. 26).

FDA Table 24. Changes in Incidence of SAEs by COSTART Term in the 'Final Safety Update' Versus the 'Pre-Approval Update' for Cohort 9 (Adapted from Sponsor Table 13, Ref. 2, pg. 26)

**Appears This Way
On Original**

Final Update of Rasagiline ISS Cohort No. 9: All Parkinson's Disease Patients Ever Exposed to Rasagiline	Revised Dictionary				Difference (%)
	Final Update Rasagiline (N=1361, Patient-Years=2646)		Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)		
	No. of Patients	% of Patients	No. of Patients	% of Patients	
ACCIDENTAL INJURY	42	3.1	32	2.4	0.7
EXTRAPYRAMIDAL SYNDROME	18	1.3	10	0.7	0.6
FALL	21	1.5	15	1.1	0.4
HERNIA	11	0.8	6	0.4	0.4
PROSTATIC CARCINOMA	16	1.2	11	0.8	0.4
CHEST PAIN	13	1.0	10	0.7	0.2
INFECTION	12	0.9	9	0.7	0.2
DEEP THROMBOPHLEBITIS	8	0.6	5	0.4	0.2
DEHYDRATION	14	1.0	11	0.8	0.2
CONFUSION	10	0.7	7	0.5	0.2
HALLUCINATIONS	8	0.6	5	0.4	0.2

*Most common SAEs in the Final update sorted by the difference in incidence of 'Final' vs. 'Pre-Approval' update (at least 0.2% difference)

Reviewer comment: I reviewed the sponsor's Table 12, Post-Text Table 8 as well as the table above, and confirmed that the differences in the risk and rate of SAEs by body system and individual AEs were small compared to the previous safety report.

As noted within initial NDA review, accidental injuries and falls remain one of the most common AEs reported with rasagiline use. (In the placebo-controlled portion of the monotherapy trial, falls were reported in 4.7% of rasagiline-treated subjects and 2.6% of placebo subjects [Ref. 10, pg. 69]).

5.3.2 SAEs in the Pharmacovigilance Database

In addition to the SAEs included in the CRF database (summarized above), Teva stated that 53 SAEs in 47 patients were found only in the pharmacovigilance⁴⁰ database as of May 15, 2005 (not including the nine deaths discussed in Section 5.2 of this review). These 53 SAEs are summarized in the table below.

FDA Table 25: SAEs in the Pharmacovigilance Database (as of May 15, 2005)(Adapted from Sponsor Text, Ref. 2, pg. 27)

# Subjects	Subject IDs	Summary
Cardiac		

⁴⁰ Teva does not specifically state what pool of subjects the pharmacovigilance database represents. However, it appears to be composed of postmarketing safety reports.

2 Patients	TVP-1012/135 #433 TVP-1012/135 #3	<ul style="list-style-type: none"> 87-year-old man with a history of ischemic heart disease, cardiac arrest, pacemaker implantation and congestive heart failure, underwent a cardiac catheterization for chest pain/abnormal dobutamine stress test, with subsequent elective defibrillator implant 80-year-old man with hypertension, hyperlipidemia and impaired left ventricular function hospitalized with atrial fibrillation and congestive heart failure. Subsequent angiography found coronary artery disease.
CVAs		
3 Patients	TVP-1012/124 #20401 TVP-1012/233 #23 TVP-1012/233 #77	<ul style="list-style-type: none"> 77-year-old with hypertension (by history, unmedicated) and hypercholesterolemia, reported transient right arm weakness 71-year-old with history of hypertension 81-year-old with diabetes, hypertension, hypercholesterolemia and prior TIA diagnosed with left carotid artery aneurysm <p>Teva reported that none of these patients had elevated blood pressure reported in association with the SAE.</p>
Vascular SAEs		
3 Patients	TVP-1012/135 #189 TVP-1012/135 # 674 TVP-1012/124 #17301	Two reports of deep vein thrombosis leading to pulmonary embolism; one report of brachial artery thrombosis due to traumatic arterial lesion.
Cancer		
3 Patients	TVP-1012/135 #640 TVP-1012/233 #38 TVP-1012/233 #42	<ul style="list-style-type: none"> Breast cancer Adenocarcinoma of the duodenum Bladder Cancer/T-Cell Leukemia^a
Fall Resulting in Injury		
8 Patients	TVP-1012/135 #53, 276, 348, 484 [2 SAEs], 629 and TVP-1012/233 #271, 290 [2 SAEs], 322	Teva summarized the 10 SAEs among 8 patients as mostly fractures, with one skin laceration and one concussion.
Nervous System SAEs		
3 Patients	TVP-1012/135 #117 TVP-1012/135 #623 TVP-1012/233 #270	<ul style="list-style-type: none"> Restless legs syndrome and leg pain Worsening PD and axonal polyneuropathy Sleep disturbance and weakness
Elective Surgery		
11 Patients	TVP-1012/135 #197, #217, #267, #412, #414, #448, #470, #481 and	The surgeries included orthopedic procedures, two deep brain stimulator implants and one transurethral resection of the prostate.

	TVP-1012/233 #38, 53, 120)	
Miscellaneous		
18 Patients	TVP-1012/135 #2	Severe constipation
	TVP-1012/135 #449	Urinary tract infection with delirium
	TVP-1012/135 # 431	Recurrent nephrolithiasis
	TVP-1012/135 #53	Admitted for pain control of multiple pelvic stress
	TVP-1012/135 #179	Osteoporosis with vertebral compression fractures and back pain
	TVP-1012/135 #180	Dysphagia and dehydration one week after rasagiline was stopped in anticipation of DBS ^b implant. PEG tube placement was followed by urinary tract infection, psychosis and delirium.
	TVP-1012/135/#201	Small bowel obstruction and pneumonia
	TVP-1012/135 #475	Cellulitis of the right arm
	TVP-1012/233 #44	Benign prostatic hypertrophy with acute urinary retention and urosepsis. Underwent a transurethral prostate resection complicated by post-procedure hemorrhage.
	TVP-1012/233 #53	Diverticulitis
	TVP-1012/233 #120	Gallstone pancreatitis
	TVP-1012/233 #407	Hypotension and syncope related to possible dehydration and gastritis/gastrointestinal bleeding
	TVP-1012/135 #348	Postural hypotension and syncope which resolved with discontinuation of pergolide
	TVP-1012/233 #553	Negative cardiac evaluation for chest pain
	TVP-1012/233 #620	Esophageal spasm. Admitted to rule out cardiac etiology
TVP-1012/233 #303	Aspiration pneumonia	
TVP-1012/233 #295	Aspiration pneumonia	
TVP-1012/233 #286	Lobar pneumonia	

a. Teva stated that this patient was reported in the CRF database as having bladder cancer, but in the pharmacovigilance database as having both the bladder cancer and a concurrently diagnosed T-cell lymphocytic leukemia.

b. DBS=Deep Brain Stimulator

5.4 Discontinuations

5.4.1 Discontinuations due to Physician/Patient Decision

Discontinuations initially attributed by the sponsor to physician/patient decision are re-examined in Section 3.5 above (among the DNP's follow-up questions to Teva subsequent to the December 7, 2005 meeting).

5.4.2 Discontinuations due to Adverse Event

Up to the database lock date (February 15, 2005), discontinuations recorded in the CRFs as “due to AE” were reported for 171 (12.6%) of all PD patients ever exposed to rasagiline (Cohort 9), as compared to 154 (11.3%) in the previous safety update. Teva reported that the most common body system associated with early termination (ET) was the nervous system (5.6%), followed by body as a whole (3.1%), the cardiovascular system (2.9%) and the digestive system (2.4%). When data from the current update was compared to the previous safety update by descending order of difference, the sponsor found no notable difference in time-adjusted frequency of AEs resulting in early termination. During the entire rasagiline clinical program, the most common AE resulting in early termination for Cohort 9 was hallucinations (1.5%, time-adjusted frequency 1.0 report/100 PYs), which Teva noted is a known side effect of dopaminergic therapy (Ref. 2, pg. 29).

FDA Table 26: Time-Adjusted Frequency of AEs Resulting in Early Termination by COSTART Term and Descending Order of the Difference* of ‘Final Update’ vs. ‘Pre-Approval’ Update (Adapted from Sponsor Table 14, Ref. 2, pg. 29)

Final Update of Rasagiline ISS Cohort No. 9: All Parkinson’s Disease Patients Ever Exposed to Rasagiline	No. of Reports Per 100 Patient Years (Revised Dictionary)		
	Final Update Rasagiline (N=1361, Patient-Years=2646)	Pre-Approval Update Rasagiline (N=1361, Patient-Years=2362.5)	Difference
CONFUSION	0.2	0	0.2
HALLUCINATIONS	1.0	0.9	0.1
ACCIDENTAL INJURY	0.2	0.1	0.1
ANXIETY	0.2	0.1	0.1

*AEs with a higher time-adjusted frequency in the Final Update database

Reviewer comment: *The rate of discontinuations due to accidental injury and anxiety in the table above is two-fold higher than in the prior safety report, although the absolute difference is very small (0.1). In the initial NDA review (Ref. 7), anxiety led to the discontinuation of 0.1% of all subjects exposed to rasagiline. However, as an adverse event during the placebo-controlled monotherapy trial, anxiety was reported in fewer rasagiline-treated subjects (2.0%) than placebo subjects (3.5%). In the placebo-controlled trial of rasagiline as an adjunct to levodopa, anxiety was reported by less than 1% of rasagiline-treated subjects (Ref. 7, pg. 141).*

5.4.3 Summary of New Discontinuations

Teva noted the following nervous system AEs leading to discontinuation:

1. **TVP-1012/135 #40624.** This 52-year-old man receiving LD and ropinirole reported hyperactivity in August 2003, and was withdrawn in December 2003, after 728 days on rasagiline, due to paranoid reaction.
2. **TVP-1012/135 #47424.** This 56 year-old-man receiving LD, amantadine and entacapone was treated for panic attacks with sertraline. One year later, he was treated for anxiety with alprazolam, paroxetine, trazodone and sertraline without improvement. The patient was discontinued from the study because treatment of his anxiety required a drug disallowed by the study protocol.
3. **TVP-1012/135 #581:** This 83-year-old woman receiving LD discontinued due to periods of confusion.
4. **TVP-1012/233 #212:** This 82-year-old woman receiving LD, metoprolol and mirtazipine, entered the study with a history of anxiety and depression. She reported a “catatonic experience,” hallucinations and confusion in She was withdrawn from the study in November 2004 due to increased confusion.
5. **TVP-1012/233 #613:** This 60-year-old woman with a history of depression was treated with LD, entacapone, amantadine, paroxetine, lorazepam and atenolol. She was hospitalized for increased anxiety, confusion and hallucinations, with sleep disturbance, anxiety, confusion and hallucinations previously reported. The study drug was discontinued and her condition improved following modification of her other PD medications and the addition of olanzapine.

Other new discontinuations due to AE listed in the CRF database included (Ref. 2, pg. 31):

6. **TVP-1012/135 #203:** This 76-year-old man with history of thoracic spondylosis, lumbar laminectomy and fusion discontinued the study due to worsening back pain.
7. **TVP-1012/135 #654:** This 69-year-old man discontinued due to “slightly low red blood cell count”/anemia. The patient’s hemoglobin and hematocrit were within normal range, but his RBC count was $4.4 \times 10^6/\text{cumm}$ at termination (normal range $4.6\text{-}6.2 \times 10^6/\text{cumm}$), with a lowest value during the study of $4.15 \times 10^6/\text{cumm}$. Teva noted that the patient entered the core study with a RBC count of $4.25 \times 10^6/\text{cumm}$ (Screening Visit).
8. **TVP-1012/135 #729:** This 64-year-old man was withdrawn due to colon cancer.
9. **TVP-1012/233 #47:** This 82-year-old man on multiple medications discontinued the study drug in February 2004, due to a persistent elevation in GGT⁴¹ and LDH⁴².

⁴¹ GGT = Gamma-glutamyl transferase

⁴² LDH = Lactate dehydrogenase

Teva stated that seven discontinuations due to AE were reported since the CRF database lock date (February 16, 2005) until May 15, 2005, as summarized below (Ref. 2, pg. 30):

1. **TVP-1012/135 #200:** This 72-year-old man, treated with LD, amantadine, quetiapine, citalopram, diazepam and donepezil, had previously reported AEs of depression, anxiety, cognitive decline, intermittent confusion and psychosis. He discontinued due to a severe psychiatric conversion reaction manifested by hyperventilation and breath holding.
2. **TVP-1012/135 #491:** This 61-year-old man treated with LD, amantadine and pramipexole was withdrawn due to increased motor fluctuations as well as worsening of depression and compulsive behavior.
3. **TVP-1012/135 #623:** This 70-year-old woman was withdrawn due to deterioration of PD (increased dyskinesia).
4. **TVP-1012/135 #640:** This 63-year-old woman withdrew due to breast cancer.
5. **TVP-1012/233 #38:** This 73-year-old man withdrew due to duodenal adenocarcinoma.
6. **TVP-1012/233, #249:** This 57-year-old man with a history of depression on LD/CD, entacapone, benzhexol, pramipexole, paroxetine, amitriptyline, lorazepam, gabapentin and zolpidem was withdrawn due to increased depression.
7. **TVP-1012/233 #407:** This 85-year-old woman withdrew due to persistent abdominal pain following a hospitalization for gastritis.

5.4.4 Expedited SAE Report: Thrombocytopenia

Teva stated that an expedited SAE report was filed in December 2005 for a possible drug-induced thrombocytopenia, which resulted in early termination (Ref. 2, pg. 31).

TVP-1012/233#166: This 81-year-old man with a history of coronary artery disease, congestive heart failure, cardiac pacemaker, diabetes mellitus, renal insufficiency, bilateral lower extremity neuropathy and polycythemia, developed thrombocytopenia. During the first six years of rasagiline treatment, his platelet counts ranged from 148 to 181 x 10³/uL. In December 2004, his platelet count dropped to 68 x 10³/uL, then decreased further to 35 before increasing to 104 x 10³/uL. ANA was mildly elevated, but lupus antibody panel was negative. Liver function was normal and there was no hepatosplenomegaly. Bone marrow showed no infiltrative/malignant process and no myelodysplasia. Iron stores were absent. A hematologist recommended discontinuing the study drug due to consideration of a drug-induced thrombocytopenia. It is noted that the patient

was taking several concomitant medications (e.g., glimepiride, allopurinol and digoxin) whose labeling list thrombocytopenia as a potential serious adverse effect. Study drug was discontinued on October 4, 2005. On — the patient received IVIG (intravenous immunoglobulin) for neuropathic pain due to bilateral lower extremity neuropathy present since 2001. A repeat platelet count on November 2, 2005, was $121 \times 10^3/uL$ (Ref. 2, pg. 32).

Reviewer comment: The rasagiline review to date has not revealed a pattern of thrombocytopenia with rasagiline usage. In addition, the subject has a complicated medical history and several concomitant medications that could contribute to the thrombocytopenia. However, this case warrants continued monitoring for similar events.

5.4.5 Other Events of Clinical Importance

Teva noted the following AEs as potentially clinically significant:

- **TVP-1012/135 #605:** This 74-year-old man experienced the SAEs of anemia, thrombocytopenia, disseminated intravascular coagulation (DIC) and rhabdomyolysis. He was found lying on the floor of his bathroom two days after a fall. His CPK on admission was 11,977 U/L. The patient was also found to be experiencing dehydration, skin breakdown and staphylococcal septicemia when found, which Teva asserted then led to acute renal failure, hypotension, DIC, anemia and thrombocytopenia. He recovered and continued the study.
- **TVP-1012/135 #33:** This subject was diagnosed with leukopenia, which resolved without change in the study drug.
- **TVP-1012/135 #73:** This subject, with a history of idiopathic thrombocytopenic purpura, was diagnosed with thrombocytopenia during the study. Teva stated that this “occurred without change in the study drug.”

Reviewer comment: It is unclear whether the phrase in quotes above means that the thrombocytopenia resolved while the subject was still receiving the study drug.

6. OTHER REMAINING SAFETY ISSUES

6.1 Rhabdomyolysis

6.1.1 FDA Comment

“You have proposed an elevation of CPK of 10 times the baseline as one criterion for deciding that a post-marketing case should be reported as a 15 day report of rhabdomyolysis. We request that you change this criterion to include a change of five times the baseline or greater.”(FDA Approvable Action Letter, July 2004)

Reviewer comment: *The sponsor re-visited this issue of rhabdomyolysis without a specific FDA request since the Approvable action letter of July 2004 to do so.*

6.1.2 Sponsor Response

Teva accepted⁴³ the reduction in the CPK threshold from a ten-fold to a five-fold elevation over baseline. With this modification, Teva proposed the following criteria for Postmarketing 15-day "alert reports" for suspected myopathy or rhabdomyolysis:

1. **CPK:** Five-fold elevation of CPK concentration from baseline levels as a sole criteria or elevated CPK values (irrespective of the level) accompanied or not by myalgia with one or more of the following:
 - Acute or acute on chronic renal failure
 - Hyperkalemia
 - Hyperphosphatemia
 - Metabolic acidosis
 - Hypocalcemia
 - Hypercalcemia
2. **Uric Acid:** Recent elevation of uric acid from baseline
3. **Other:** Any other case assessed by the reporter or company's medical reviewer as suggestive of myopathy or rhabdomyolysis

Reviewer comment: *The above criteria for identifying potential cases of rhabdomyolysis or other myopathies are acceptable. As the goal of safety monitoring is to capture as many cases as possible, the broader criteria for potential cases are appropriate.*

6.2 Thorough QT Study

In their submission of March 17, 2006 (Ref. 6), Teva stated they would conduct a "thorough QTc study characterizing the effects of rasagiline on cardiac repolarization in humans" in Phase IV. Teva estimated the date of the protocol submission as _____, with study start predicted in _____ / and a final study report expected in _____ (Ref. 6 and 7).

Reviewer comment: *Given that the existing data on rasagiline's effect on cardiac repolarization is relatively unremarkable, I believe it is acceptable for this study to be performed in Phase IV. I consider this study necessary, however, as the QT data collection and analysis in the rasagiline development program does not meet current*

⁴³ These statements were taken from the "Other Clinical Comments" section of Teva's Ref. 1.

guidelines for a thorough QT study, and the understanding of rasagiline's potential effect on cardiac repolarization would be improved by doing so.

*Teva's proposed timeline estimates that the final study report should be finished by —
— This seems somewhat lengthy, given that the study can likely be completed within a few months. Teva should be encouraged to conduct and analyze the data as soon as possible..*

7. DISCUSSION AND CONCLUSIONS

***Reviewer comment:** Comments and conclusions on the few non-melanoma safety issues addressed in this review are contained within their respective section of the review.*

7.1 Overall Melanoma Conclusion

The occurrence of melanomas within the rasagiline development program has led the DNP to conduct an extensive examination of whether these melanomas represent more cases than one would expect for the development program population, thus implicating a causal role for rasagiline. As most of the cases were diagnosed during open-label extension studies, no parallel control group was available for comparison. The analysis was further complicated by variation in melanoma risk among studies due to geographic differences, rising rates of melanoma worldwide and surveillance bias from the institution of an active dermatologic screening while the phase III rasagiline clinical trials were in progress.

The foundation of the FDA's analysis has included the following:

- **Comparison with Cancer Registry Data:** The rate of melanomas within the rasagiline development program was initially compared to the melanoma rate within the SEER⁴⁴ cancer registry. Although the melanoma rate in the rasagiline development program was found to be higher, this comparison is confounded by the presence of active screening for melanoma in the rasagiline development program, and evidence of underreporting of melanomas within the SEER registry.
- **Comparison of a Sponsor PD Cohort Study (EP002) to the AAD⁴⁵ Skin Cancer Screening Program Data:** The EP002 cohort was composed of North American PD patients who had **not** been exposed to rasagiline, and the AAD Skin Cancer Screening Program was a voluntary skin screening program conducted in the general community. The particular value of this comparison is that both populations were undergoing screening for melanoma. When the rates for the AAD data are applied in an age- and gender-matched basis to the EP002 cohort, the observed to expected ratio is elevated, as shown in the table below.

⁴⁴ SEER = Surveillance, Epidemiology and End Results

⁴⁵ AAD = American Academy of Dermatology

FDA Table 27: 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 ⁴⁶
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

Because the primary difference between the AAD screening population and the EP002 population was the presence of PD in the EP002 patients, this data is consistent with an association between melanoma and PD itself or its non-rasagiline treatments.

- **Comparison to Other PD Development Programs:** The primary limitation of this comparison is that other PD development programs were not conducting active surveillance for melanoma cases. Notably, the rate of melanoma in the rasagiline development program is still elevated compared to the other PD development programs when the rate in the rasagiline development program is calculated only from the cases diagnosed prior to initiation of the dermatologic screening program; however, the 95% confidence intervals overlap between the various rasagiline scenarios and the other PD treatments (See Section 4.3 of this review.)
- **Dose Response Analysis:** Various dose response analyses, using different methods to assign cases to dose (i.e. modal dose, highest dose, dose at diagnosis), have failed to show a pattern of increasing melanoma rate with increasing doses of rasagiline.
- **Melanoma Rates with Continuing Rasagiline Exposure:** Observation of the rate of melanoma with longer duration of rasagiline use (or greater cumulative exposure) has not shown a strong pattern of higher rates with continued exposure, as one would expect of a carcinogen. This analysis, however, is confounded by

⁴⁶ 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>.

the timing of the beginning of the dermatologic screening program, with peak melanoma diagnosis rates at the beginning of the PRESTO study and end of the TEMPO study based upon when screening began relative to the start of the respective studies. It is also confounded by patient discontinuation over time.

Overall, I consider the melanoma data to date as insufficient to either confirm or refute an association with rasagiline. I therefore continue to believe that the most appropriate method for the better understanding of any relationship between rasagiline and melanoma is through the conduct of a Phase IV melanoma study, such as the one described in the sponsor protocol submitted for this review. Until results from such a study are available, the labeling should contain an adequate description of and caution regarding the melanomas observed during the rasagiline development program (Proposed labeling included in Attachment 8.3).

Proposed safety-related labeling for rasagiline builds off the labeling sent with the first approvable letter and represents the contributions of this reviewer along with Dr. Judy Racoosin, DNP safety team leader for rasagiline; it can be found in Appendix 8.3.

**APPEARS THIS WAY
ON ORIGINAL**

8. ATTACHMENTS

8.1 Minutes from December 7, 2005 Melanoma Meeting with Sponsor

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2005
TIME: 11 AM – 12 Noon
LOCATION: WO Bldg. #22, Conference Room 1419
APPLICATION: NDA 21-641 Rasagiline
TYPE OF MEETING: End of Review
MEETING CHAIR: Dr. Temple

FDA ATTENDEES, TITLES, AND DIVISION

Dr. Robert Temple – Office Director, ODE 1
Dr. Russell Katz – Division Director, HFD-120
Dr. John Feeney – Group Leader, HFD-120
Dr. Judith Racoosin – Safety Team Leader, HFD-120
Dr. Lisa Jones – Safety Reviewer, HFD-120
Dr. Paul Roney – Pharmacology & Toxicology Reviewer
Dr. Lois Freed – Pharmacology & Toxicology Supervisor
CDR Teresa Wheelous – Sr. Regulatory Management Officer, HFD-120

TEVA Pharmaceutical Industries, LTD ATTENDEES AND TITLES:

Teva Neuroscience

Rivka Kreitman, Ph.D, Vice President, Innovative Research and Development
J. Michael Nicholas, Ph.D., Senior Director of Regulatory Affairs
Dennis Williams, R.Ph, Sr. Manager, Regulatory Affairs

Teva Israel

Michal Herskovitz, ChemEng, Senior Director, Global Regulatory Affairs
Ruth Levy, Ph.D., Executive Director, Global Pipeline Development
Noa Leibovitch, Ph.D., Associate Director, Global Pipeline Development
Yael Keenan, Ph.D., Associate Director, Global Clinical Research
Galia Shifroni
John Ienni
Tami Yardeni

BACKGROUND AND MEETING OBJECTIVES:

The purpose of the meeting is to discuss the melanoma issues raised in the August 4, 2005 approvable letter.

DISCUSSION POINTS:

- The Teva representatives commenced by stating that their goal for the meeting was to answer any remaining FDA questions regarding rasagiline and melanoma. Teva then reviewed their responses (sent via e-mail December 7, 2005 [the morning of the meeting]) to a series of previous FDA questions on the meeting briefing material (see Appendix). As a follow-up to a question regarding the effect of discontinuing subjects on melanoma rates by duration of exposure, Teva stated that subjects who did and did not discontinue had similar melanoma risk factors.
- In a discussion of the dose-response analysis, the merits and limitations of different methods for ascertaining subject dose (i.e. modal, highest dose, etc.) were reviewed. Dr. Katz stated that it was his understanding that the modal dose represented all or the large majority of a subject's exposure in most cases. Dr. — stated that Teva had also performed a dose-response analysis by cumulative dose, which the FDA had not yet seen. Teva then shared the results of the cumulative dose analysis. The results were not dissimilar from other dose analyses that have been conducted (e.g. the highest rate was in the lowest cumulative dose category, the lowest rate was in the second lowest cumulative dose category, with rising rates over subsequent higher cumulative dose categories).
- Dr. Feeney asked the Teva representatives for their thoughts on the FDA comparison of the sponsor's EP002 cohort study and the American Academy of Dermatology (AAD) melanoma screening data, as Teva had not addressed this analysis in their meeting briefing materials. Teva stated that there was insufficient time before the meeting for a full evaluation, but that the comparison appeared to be supportive of a relationship between Parkinson's disease and melanoma. Dr. Rigel noted that he was involved in the AAD screening program and that approximately 20% of subjects had more than one screening, which differed from the population in the EP002 study.
- Regarding a Phase IV, large simple trial, Teva stated that performing a placebo-controlled study would be difficult. Dr. Temple asked why this was so, and Teva stated that physicians are less likely to enroll patients in placebo-controlled studies. Dr. Temple noted that, except for rasagiline, the proposed study would allow subjects to follow whatever treatment regimen their physician recommended. Dr. Temple believed physician reluctance to enroll patients would be reduced if this was clearly communicated. Teva stated that study planning was ongoing.

- Dr. — stated that the FDA’s comparison of the melanoma rate in the rasagiline development program to the melanoma rate in other Parkinson’s disease (PD) development programs was confounded by the dermatologic examinations in the rasagiline development program. Dr. Katz noted that when the comparison was limited to only the melanomas diagnosed prior to the screening program, rasagiline still had a higher rate than other PD development programs. Dr. — stated that three of the six pre-screening melanomas should arguably not be included as cases, reportedly because one of the cases was diagnosed very early during rasagiline treatment (and thus assumed to be a preexisting lesion), and the other two were reported after a “Dear Healthcare Provider” letter was sent to investigators describing the melanoma cases in the development program (we are waiting on confirmation from the sponsor that these were their reasons for excluding the three cases).
- The Division agreed to provide Teva with a list of follow-up questions resulting from discussion at the meeting. These questions were sent on December 9, 2005. These questions follow below:

1. Please submit an analysis comparing melanoma risk factors and other melanoma-relevant demographic factors (notably, age and sex) for the cohorts of continuing and discontinuing subjects in TEMPO and PRESTO (for each study separately). For TEMPO, in particular, another melanoma-relevant factor that should be compared for the continuation and discontinuation cohorts is the addition of L-dopa therapy

Due to screening initiation and other melanoma awareness activities, the comparison should be performed at various time points, assessed as both time from study start (for example, at six months, 12 months, 24 months, 36 months) and time by calendar year (for example, all subjects, regardless of time in study, before and after commencement of dermatologic screening.)

2. In the briefing packet, you noted that several programming errors affected some of the results previously provided (pg. 6). Please provide a version of Table 19 below using the corrected data. You should have already received this table as part of the shared FDA melanoma review, but it is also included below for your convenience.

FDA Table 19 (pg. 35): 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%)

3. Regarding the number of melanoma cases which should be included in the pre-screening melanoma rate calculation:

(a) The briefing packet noted that there were six melanomas (4 in situ and 2 invasive) identified prior to initiation of mandatory dermatological screening (pg. 11). At the meeting there was discussion that the more appropriate case count is three melanomas. Assuming that you would exclude the advanced melanoma occurring two months after study initiation, which other melanoma cases do you believe should not be included among the six pre-screening cases (i.e., which other two cases occurred after the "Dear Investigator" letter and before screening began?)

(b) To clarify, were there melanoma awareness measures (the "Dear Investigator" letter along with the Investigator Brochure) prior to the initiation of screening? What were the approximate dates for these measures and the initiation of screening? Is there any evidence that the pre-screening melanoma awareness activities resulted in heightened melanoma detection?

4. At the meeting, a dose-response analysis using cumulative dose was shown. Please provide us with the results of this analysis (including confidence intervals for the point estimates).

An additional note regarding the safety update:

Within the section on patient discontinuation, for patients who discontinued for reasons of "physician decision" or "patient decision", please examine the case report form and any other available information for underlying reasons for discontinuation (and include that information, where identified).

Appendix: Teva Responses to DNP Questions on the Pre-Meeting Briefing Package

1. In the Dose-Response analysis, which cases were included in the "0 mg" group? Were cases of melanoma found prior to treatment initiation included? As the purpose of the analysis is to examine treatment-emergent cases, only cases in subjects actually treated with placebo should be included in the "0 mg" group.

Response: Only placebo case (treatment emergent) in the LARGO study is included. This is patient number 41604 in attachment 2 of the briefing book.

2. In the Dose-Response analysis, how was the person-time (denominator) distributed among the various doses the subjects were exposed to? For example, if a patient was treated with 0.5 mg initially and then later increased to 1 mg, was the time they were treated with each dose allotted to that dose?

Response: actual dose was allocated to each dose. In the above example, this patient attributes exposure to both doses proportionally to time spent on applicable dose.

3. Could a copy of Figure 1 (pg. 8) with the number of cases and person-time included be provided?

Response: Post-Text tables 2, 3, 4 in the briefing book provide the number of cases and person-time.

4. On page 10 (Delayed vs. Immediate Start Analysis), it is stated that "Comparison of each time strata from initial rasagiline start...demonstrates that CIs for immediate and delayed starters have a substantial overlapping and the p values are insignificant." Which time strata are referred to in this statement?

Response: The CI of incidence rates between Presto immediate and Presto delayed, Tempo immediate and Tempo delayed, and total immediate and total delayed in any time point overlap as presented in post text tables 9 and 10 of briefing book.

5. Given that the rate of melanoma over time is affected by dropouts, did you do any melanoma surveillance of subjects who discontinued from the rasagiline open extension studies?

Response: Subjects who discontinued the open extension studies did not have follow-up examinations.

6. Your submission stated that you would investigate the feasibility of the phase IV trial design and provide additional information in advance of the meeting. Are there additional pre-meeting details on the melanoma Phase IV study design?

Response: We are still investigating the feasibility of trial designs. A synopsis for a randomized large simple trial is attached.

SYNOPSIS

Protocol Title	A Multicenter Simple Randomized Study to Compare the Ratio of Melanoma Incidence Rates Between PD Patients who are Exposed or Unexposed to Rasagiline
Participating Countries	USA, Canada and possibly Australia
Clinical Phase	Post-approval, Phase IV
Investigational Medicinal Product (IMP) & Dosage	Oral: rasagiline 1mg, administered once a day
Study Duration	To be determined
Study Population	Idiopathic PD patients
Study Objective	To compare melanoma rates between PD patients who are treated or untreated with rasagiline and to demonstrate similar melanoma incidence rates between rasagiline and non-rasagiline arms.
Study Design	<p>PD patients who need initial PD therapy, dose adjustment or additional therapy with any anti-PD medications at baseline will be randomized in 1:1 ratio to 2 arms:</p> <ol style="list-style-type: none"> 1. Rasagiline arm 2. Non-rasagiline arm <p>The use of PD therapy will be allowed in both treatment arms</p> <p>During the study, in addition to study drugs, additional concomitant PD therapy will be allowed. Adjustment of all PD therapy dose regimens will be allowed at any time during the study. All PD concomitant therapy will be used according to drug labeling.</p> <p>Subjects will undergo dermatologic examination at baseline and every 6 months thereafter, by a certified dermatologist, who will be blinded as to study randomization arms. Any suspicious lesion will be considered for a biopsy, at the discretion of the dermatologist. Slides of all biopsy specimens will be evaluated by a central dermatopathologic facility, without exposing the treatment assignment. Subjects who are diagnosed with melanoma (in situ or invasive) at baseline will not be included in the study and those who are diagnosed with melanoma after randomization will immediately terminate the study.</p>
Outcome Measure and analysis methods	Melanoma incidence rate of combined in situ and invasive cases
Statistical methods:	The primary analysis to demonstrate similar MM rates will be based on non-inferiority approach. Poisson Regression (SAS® Proc GENMOD), will be used, to provide the upper limit of the one-sided 95% confidence interval (CI) for the risk ratio of having melanoma. The criterion for non-inferiority will be the upper limit of the 95% CI less than 2. The model will include Center, PD and demography characteristics (age, gender, PD duration, LD treatment).
Sample size:	It is expected that several thousand patients will be enrolled to the study. The exact number will be determined.
Data Safety Monitoring Board	An independent Data Safety Monitoring Board will be established prior to study initiation in order to manage all safety concerns of the study. The role of this committee will be to oversee the emerging safety data of the study by multiple interim reviews. Stopping rules due to meeting the study objective, non-inferiority, or alternatively: futility, inferiority or any safety aspects in the interest of the study subjects will be pre-defined in the study protocol

Inclusion/Exclusion Criteria	<p><u>Main Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Willing and able to give informed consent. 2. Men and women with confirmed diagnosis of idiopathic PD, who will require initial PD therapy, dose adjustment or additional therapy with any anti-PD medications at the time of randomization. <p><u>Main Exclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Patients who have taken any experimental medications within 60 days prior to baseline. 2. Patients previously exposed to rasagiline 3. Patients diagnosed with melanoma based on the baseline dermatology examination. Patients with suspicious lesions at baseline who do not undergo biopsy.
------------------------------	--

Appears This Way
On Original

8.2 FDA QUESTIONS TO TEVA: FOLLOW-UP FROM DECEMBER 7TH MEETING DISCUSSIONS

As mentioned at our meeting on December 7, 2005, below are several follow-up questions pertaining to the melanoma analysis.

1. Please submit an analysis comparing melanoma risk factors and other melanoma-relevant demographic factors (notably, age and sex) for the cohorts of continuing and discontinuing subjects in TEMPO and PRESTO (for each study separately). For TEMPO, in particular, another melanoma-relevant factor that should be compared for the continuation and discontinuation cohorts is the addition of L-dopa therapy

Due to screening initiation and other melanoma awareness activities, the comparison should be performed at various time points, assessed as both time from study start (for example, at six months, 12 months, 24 months, 36 months) and time by calendar year (for example, all subjects, regardless of time in study, before and after commencement of dermatologic screening.)

2. In the briefing packet, you noted that several programming errors affected some of the results previously provided (pg. 6). Please provide a version of Table 19 below using the corrected data. You should have already received this table as part of the shared FDA melanoma review, but it is also included below for your convenience.

FDA Table 19 (pg. 35): 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%)

3. Regarding the number of melanoma cases which should be included in the pre-screening melanoma rate calculation:

(a) The briefing packet noted that there were six melanomas (4 in situ and 2 invasive) identified prior to initiation of mandatory dermatological screening (pg. 11). At the meeting there was discussion that the more appropriate case count is three melanomas. Assuming that you would exclude the advanced melanoma occurring two months after

study initiation, which other melanoma cases do you believe should not be included among the six pre-screening cases (i.e., which other two cases occurred after the "Dear Investigator" letter and before screening began?)

(b) To clarify, were there melanoma awareness measures (the "Dear Investigator" letter along with the Investigator Brochure) prior to the initiation of screening? What were the approximate dates for these measures and the initiation of screening? Is there any evidence that the pre-screening melanoma awareness activities resulted in heightened melanoma detection?

4. At the meeting, a dose-response analysis using cumulative dose was shown. Please provide us with the results of this analysis (including confidence intervals for the point estimates).

An additional note regarding the safety update:

Within the section on patient discontinuation, for patients who discontinued for reasons of "physician decision" or "patient decision", please examine the case report form and any other available information for underlying reasons for discontinuation (and include that information, where identified).

Appears This Way
On Original

16 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓
___ § 552(b)(4) Draft Labeling

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

/s/

M. Lisa Jones
5/3/2006 01:19:11 PM
MEDICAL OFFICER

Judith Racoosin
5/3/2006 02:56:30 PM
MEDICAL OFFICER