

Review and Evaluation of Clinical Data
Safety Team Leader Review of Selected Safety Issues in the
NDA Safety Database

NDA: 21-641

Drug: rasagiline (AGILECT®)

Route: oral

Indication: Parkinson's disease- monotherapy and levodopa adjunctive treatment

Sponsor: Teva

Action Date: 7/5/04

1 Background

Dr. Jones has provided a thorough review of the safety experience with rasagiline. In this memo I will address only selected safety issues that require additional discussion.

As described in more detail in Dr. Jones' review, Cohort 1 refers to the participants in the rasagiline monotherapy controlled trials, Cohort 2 refers to the participants in the rasagiline adjunctive treatment controlled trials, and Cohort 9 refers to the group of all patients exposed to rasagiline therapy.

2 Safety issues in the rasagiline NDA database

2.1 General NDA issues

2.1.1 ECG

In the rasagiline development program, only the Cohort 2 ECGs were analyzed in the minimum standard way (i.e., a presentation of mean change from baseline for the ECG intervals and an outlier analysis for the QTc intervals). These analyses suggested little, if any, effect of rasagiline on the ECG interval durations (QTcB¹ mean change from baseline rasagiline 1.1 msec vs. placebo 0.4 msec; QTcF mean change from baseline rasagiline 2.4 msec vs. placebo 0.5 msec). More placebo than rasagiline patients shifted from non-PCS QTc values to PCS QTc values (rasagiline 1.4% vs. placebo 1.9%). Two rasagiline patients and no placebo patients had a shift to a QTc greater than 500 msec; however, one of these rasagiline patients had a paced rhythm on the last observed visit (LOV) ECG, making it difficult to interpret the QTc change.

The Cohort 1 ECGs were only analyzed to the extent of "normal" vs. "abnormal" which is totally inadequate with regard to the minimum accepted standards. Although the data from the studies of rasagiline as adjunctive therapy to levodopa in advanced Parkinson's disease (PD) were not suggestive of an effect of rasagiline on cardiac repolarization or

¹ QTcB refers to Bazett's correction (QT/\sqrt{RR}); QTcF refers to the Fridericia correction ($QT/\sqrt[3]{RR}$).

other electrocardiographic parameters, there is no way to quantitate the effect of rasagiline alone from the available data (the effect of levodopa alone on these cardiac parameters is not well defined). Therefore it is necessary to get an assessment of the effect of rasagiline monotherapy on the ECG of PD patients. We will request that the sponsor send the original ECG tracings from the TEMPO trial to be read by the group who read the Cohort 2 ECGs.

Additionally, the effect of rasagiline on the ECG in healthy volunteers was not well defined in the phase I studies. As far as I can tell, no study included ECGs timed to coincide with T_{max}. Currently in CDER, guidance is evolving to standardize the assessment of the effect of newly developed drugs on ECG parameters, particularly the QTc. A provision for a “thorough” QT study is currently being discussed, but at present there is no requirement that such a study be performed in a drug development program that is already completed (unless of course, a signal for QTc prolongation was identified in a previous study). We would propose that the sponsor, in addition to better characterizing the effect of rasagiline on cardiac repolarization in PD patients taking rasagiline as monotherapy, perform a thorough QT study to characterize the effect of rasagiline on the QTc of healthy subjects. If the analyses of the QTc interval in the monotherapy cohort patients are not suggestive of a signal of QTc prolongation, we could consider asking for the thorough QT study as a phase IV commitment. However, if other clinical pharmacology studies were required for approval (e.g., additional tyramine studies), a study conducted pre-approval could potentially include a thorough QT component.

2.1.2 Differences in reporting of AEs between US and non-US studies

In section 4.3 of her review (FDA Table 11), Dr. Jones details the differences in AE reporting between the adjunctive studies conducted in North America (PRESTO) and outside North America (LARGO). In PRESTO the proportion of rasagiline patients reporting an AE was about two times that of the proportion of rasagiline patients reporting an AE in LARGO. The same pattern was observed among placebo patients in the two trials. This pattern was observed not just for commonly occurring AEs (e.g. dyskinesia, nausea), but also for serious AEs. In this regard, the pattern of AE reporting in the rasagiline NDA safety database differs from other NDA safety databases that have shown a difference between the AE reporting frequencies in US and non-US studies². In those other NDAs, although there was a difference in the reporting of common AEs between similarly designed US and non-US studies, the incidences of serious AEs were similar.

Because of the substantial differences in common AE risks between PRESTO and LARGO, and the fact that the intended population is likely to be more like the PRESTO population (North American trial), we will request that the sponsor only report the PRESTO results in the common AE table in labeling for the adjunctive use of rasagiline.

² Refer to my memo dated 9/30/99, entitled “Is there a difference in adverse event reporting patterns in Europe as compared with the United States?”

2.2 Safety issues generally associated with pharmacological therapy of Parkinson's disease

2.2.1 Orthostatic hypotension

Orthostatic hypotension occurs commonly among PD patients. Some medical literature has suggested that autonomic dysfunction occurs later in the course of PD, but in a recently published study of newly diagnosed PD patients who were previously untreated, 14% (7/51) had a decrease of at least 20 mmHg in systolic blood pressure after standing for three minutes.³

In Cohort 1, there was no excess of AEs for postural hypotension in the rasagiline group compared to the placebo group (rasagiline 3.1%, n=9; placebo 4.6%, n=7). However, in Cohort 2, there was such an excess in postural hypotension (rasagiline 4.7%, n=18; placebo 1.3%, n=5).

When vital sign data was examined for evidence of orthostatic hypotension in Cohort 1, there was little difference between placebo and rasagiline 1 mg for differences in SBP of between 20-30 mmHg (16.6% versus 16.8% respectively). However, when considering all dose groups in Cohort 1, there was an excess of rasagiline 2 mg subjects with post-baseline supine-standing SBP \geq 30 mmHg, but no difference between the 1 mg and placebo groups (8.9%, 4.0% and 5.3% in the rasagiline 2 mg, 1 mg and placebo groups, respectively). For Cohort 2, the categorical analysis of postural hypotension based on vital sign data was consistent with the excess of postural hypotension AEs in the rasagiline treated group compared to the placebo group. The categorical analysis showed that the incidence of supine-standing SBP between 20-29 mmHg was increased in the rasagiline 1 mg group compared to placebo (24.2% versus 20.1%, respectively), and the incidence of supine-standing SBP \geq 30 mmHg was higher in the rasagiline 1 mg group compared to placebo (10.5% versus 6.7%, respectively).

Orthostatic hypotension is described in the Precautions section. The proposed labeling has been edited for clarity and to describe the timing of the episodes in relation to the treatment course.

2.2.2 Interactions with Antidepressants

Labeling for non-selective MAO inhibitors, as well as selegiline, a selective MAO-B inhibitor, includes warning statements regarding the potential for severe and sometimes fatal reactions resulting from the combination of those drugs with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). Because there were published case reports of such severe reactions resulting from the combination of selegiline and fluoxetine and selegiline and fluvoxamine, concomitant treatment with those two SSRIs was not allowed in the rasagiline clinical trials. Small numbers of

³ Bonuccelli U, Lucetti C, Del Dotto P, et al. Orthostatic Hypotension in De Novo Parkinson Disease. *Arch Neurol* 2003; 60:1400-1404.

rasagiline treated patients were exposed to other SSRIs (n=26) or TCAs (n=31). There was no evidence of severe reactions in those patients; however, the number exposed was too small to rule out an important risk associated with such combinations. As such, similar to the selegiline labeling, we will recommend in the Warning section of labeling that the concomitant use of rasagiline with TCAs or SSRIs/SNRIs be avoided.

2.2.3 Tyramine Sensitivity

Dr. Kapcala is reviewing the formal studies of tyramine sensitivity associated with rasagiline treatment. However, Dr. Jones reviewed the NDA safety database for clinical evidence of a “cheese reaction” manifesting as a hypertensive emergency.

No patients treated with rasagiline doses in the range of 0.5-2 mg exhibited evidence of a hypertensive emergency. However, two patients in a clinical pharmacology trial receiving rasagiline 10 mg had a hypertensive reaction. Dr. Jones’ summary of these patients is attached below.

1. **TVP-1012/111 #803:** This 64 year-old female experienced localized muscle cramps/dystonia on day 1 and day 22, while being treated with rasagiline 1 mg/day and 10 mg/day, respectively. On study day 22, her rasagiline dose was raised from 5 mg/day to 10 mg/day.

On study day 28, the subject experienced headache and hypertension (160/110). Her dose was decreased to 5 mg/day, although these symptoms were reported to last for two days. The subject also reported onset of vertigo on day 28, which persisted for approximately ten days.

On study day 29, the subject experienced a syncopal episode lasting two minutes, which resulted in a one day hospitalization. During the hospitalization, “a high blood-pressure” was measured, and the subject was diagnosed with hypertrophic cardiomyopathy. The study drug was discontinued at this time. The subject’s blood pressure was reported to stabilize after two days treatment with propranolol and to remain within normal range until the end of the study follow-up period.

2. **TVP-1012/111 #808:** This 58 year-old woman had a five year history of PD. Hypertension was not listed among her past medical history (asthma, appendectomy). At randomization the subject’s medications were: levodopa/carbidopa, selegiline, biperiden, bromocriptine, and alpha-tocopherol acetate.

The subject received escalating doses of rasagiline 1 mg/day (for one week), 2 mg/day (for one week). (The narrative did not mention the subject receiving 5 mg/day, but as per the protocol she presumably did so in the third week.) On day 22, the dose was increased to 10 mg/day in the fourth week.

On day 25, the subject experienced vertigo for approximately one hour, and headache, nausea and vomiting which lasted for several days. The study medication was stopped for 48 hours beginning on day 25.

On day 28, the subject developed severe headache and hypertension (220/120). A blood pressure “later on that day” was stated to be within normal range, without any pharmacological intervention. The subject’s rasagiline dose was reduced to 2 mg/day.

The events of day 28 led to the subject’s hospitalization on day 29, which lasted ten days. The study drug was permanently discontinued upon her hospital admission. After admission, the subject reported headache, mild nausea and vomiting for nine days. Hypertension was reported to have been stabilized within six days of admission following treatment with captopril, which was continued for forty days.

The subject then switched to methyldopa for ten days, and finally stopped all anti-hypertensive medications 52 days after the event occurred. From that time until the last follow-up visit (two months after stopping anti-hypertensive treatment), Teva reported the subject remained normotensive.

No information was provided in the Safety Update, the study report or the subject's case report form regarding her recent diet with respect to tyramine containing foods. Her prior study blood pressure measurements were normotensive, with standing measurements of 120/85 (Baseline), 120/80 (Week 1), 120/80 (Week 2), and 120/85 (Week 3).

The study report for TVP-1012/111 stated that patients were instructed to follow a low tyramine diet. However, no documentation regarding the individuals' diets were included.

The clinical data suggest that tyramine restriction is not necessary for patients being treated with the intended dose (1 mg). However, tyramine restriction with higher doses will have to be considered should higher doses be developed in the future. Additionally, some consideration should be given to warning patients taking inhibitors of cytochrome P450 1A2 (fluoroquinolones, fluvoxamine) to follow a low tyramine diet, due to the increased AUC of rasagiline observed with concomitant use of a fluoroquinolone.

We will defer further editing of the labeling pertaining to the tyramine/rasagiline interaction to Drs. Kapcala and Feeney who reviewed those studies.

2.2.4 Sleep Attacks

In the late 1990's a phenomenon was reported in association with dopamine agonists for the treatment of Parkinson's disease that consisted of the acute onset of sleep during activities not usually associated with the onset of sleep (e.g., driving a car, having a conversation, etc.). Dr. Jones reviewed the rasagiline database for evidence of such "sleep attacks" in patients taking rasagiline. She identified three cases that were coded as "sudden sleepiness" (n=2) or "sleep attacks" (n=1). Notably, each of these patients was taking a dopamine agonist concomitantly. Thus there is no evidence from the rasagiline clinical development program for rasagiline having an independent risk of "sleep attack" apart from that associated with dopamine agonists. However, we will request that the Office of Drug Safety monitor for such cases in the postmarketing period.

2.2.5 Hallucinations

In Cohort 1, three rasagiline-treated (1 mg/day) subjects discontinued due to hallucination, compared to none in the placebo group. In Cohort 2, two rasagiline subjects discontinued due to hallucinations compared to one in the placebo group. In Cohort 9, hallucinations led to discontinuation in 1.0% of patients (n=14). In Cohort 1, hallucinations reported as an AE associated with rasagiline treatment occurred in a small number of patients, but at a frequency twice that in the placebo group (rasagiline 1.4%, n=4; placebo 0.7%, n=1). In Cohort 2, the excess frequency of hallucinations in the rasagiline group compared to the placebo group was not as marked as in Cohort 1 (rasagiline 2.9%, n=11; placebo 2.1%, n=8). This likely reflects the increasing frequency of hallucinations associated with Parkinson's disease as it progresses.

A Precautions statement will be added in the “General” section to caution health care providers of the risk of hallucinations leading to discontinuation observed with rasagiline treatment. The proposed text follows below.

Hallucinations:

2.3 Safety issues not generally associated with pharmacological therapy of Parkinson’s disease

2.3.1 “Flu syndrome” and musculoskeletal symptoms

In Cohorts 1 and 2, “flu syndrome” and musculoskeletal symptom AEs were generally not reported as serious AEs and did not commonly lead to early discontinuation (see FDA Table 20 in Dr. Jones’ review). However, in Cohort 1, the AEs flu syndrome, fever, malaise, rhinitis, conjunctivitis, neck pain, arthralgia, arthritis, and joint disorder were all reported at least twice as frequently in the rasagiline group as in the placebo group. In Cohort 2 this rasagiline associated excess was observed for flu syndrome, neck pain, and arthralgia.

FDA Table 1. Incidence of Flu and Musculoskeletal Symptom Adverse Events in Cohorts 1 and 2

	Cohort 1				Cohort 2			
	Rasagiline (1 mg) N=149		Placebo N=151		Rasagiline (1 mg) N=380		Placebo N=388	
	# pts	% pts	# pts	% pts	# pts	% pts	# pts	% pts
Arthralgia*	11	7.4	6	4.0	12	3.2	5	1.3
Flu syndrome*	7	4.7 [^]	1	0.7	4	1.1	2	0.5
Fever	4	2.7	2	1.3	4	1.1	5	1.3
Rhinitis	4	2.7	2	1.3	2	0.5	3	0.8
Conjunctivitis	4	2.7	1	0.7	2	0.5	4	1.0
Malaise	3	2.0	0	0	1	0.3	2	0.5
Neck pain*	3	2.0	0	0	6	1.6	2	0.5
Arthritis	3	2.0	1	0.7	2	0.5	3	0.8
Joint disorder	2	1.3	1	0.7	3	0.8	4	1.0
Myalgia	2	1.3	3	2.0	2	0.5	5	1.3

*Rasagiline group has at least a two times excess in Cohorts 1 and 2.

[^]4.7% is the corrected value after gastroenteritis patients were recoded to “stomach flu”.

As Dr. Jones described in her review, the verbatim terms for “flu syndrome” generally mentioned “flu” and did not include specific symptom details (the numbers above reflect the recoding of gastroenteritis to another PT [stomach flu]). The verbatim terms coded to

the PT “arthralgia” generally described pain and/or soreness in a specific joint or joints. Among the verbatim terms coded to “arthralgia”, a few described diffuse joint pain. The verbatim terms coded to the PT “arthritis” generally included the word “arthritis” in it, or described joint inflammation. The verbatim terms coded to the PT “joint disorder” generally referred to edema, swelling, or stiffness of a joint (or herniation of a disc). Also mentioned by Dr. Jones was that there is some overlap of these AE terms among patients.

It is not immediately obvious why the excess frequency in the rasagiline group is more marked in the monotherapy cohort compared to the adjunctive therapy cohorts. In the ISS, the sponsor did not provide an explanation for this pattern of AEs. Some of the symptomatology (e.g., fever, arthralgia) suggests the possibility of an immune reaction; however, there is only a slight excess of rash in Cohort 2 (Cohort 1: rasagiline 1mg 2% [3/149] vs. placebo 3.3% [5/151]; Cohort 2: rasagiline 2.6% [10/380] vs. placebo 1.5% [6/151]) and no evidence of drug-related eosinophilia (Cohort 1: rasagiline 1 mg 0.7% [1/149] vs. placebo 0%; Cohort 2: no AE reports of eosinophilia in either group) in the rasagiline groups. Thus there is little evidence to support an immune reaction.

Dr. Jones’ examination of time to flu syndrome AE suggests that the risk is not just early in treatment; however, more detailed analyses need to be performed to adjust for patient censoring due to dropout. One consideration that needs to be evaluated is the possibility that placebo patients had amantadine added differentially from rasagiline patients. As amantadine is an antiviral agent, it could have mitigated the flu syndrome in those treated with it. We will request that the sponsor examine the distribution of patients adding amantadine, and the timing of the addition of that therapy.

We will also recommend that the sponsor examine the verbatim terms in the group of patients reporting these AEs to look for a common syndrome involving fever, arthralgia, and flu symptoms.

2.3.2 Melanoma

In section 5.0 of her NDA safety review, Dr. Jones presents a thorough discussion of the regulatory history of the melanoma issue in the rasagiline development program, along with a review of the sponsor’s position on the issue, and additional analyses to better assess the potential drug-relatedness of the melanoma cases. Please refer to her review for additional details.

2.3.2.1 Description of Cases

The cases of melanoma identified during the rasagiline development program are summarized in the following table:

Table 3. Description of melanoma cases in rasagiline clinical program

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

pc = placebo controlled
Act. = active phase

As seen in the preceding table, 20 melanomas occurred in 19 patients through the four month safety update⁴. Of the three patients who had melanoma in LARGO (122), two were diagnosed prior to treatment initiation and the third was in a placebo-treated patient. One other melanoma case in the PRESTO extension was diagnosed prior to treatment, leaving 16 melanomas occurring in 15 rasagiline treated patients (one patient had two separate lesions).

Dr. Jones summarized the characteristics of the melanoma cases as follows:

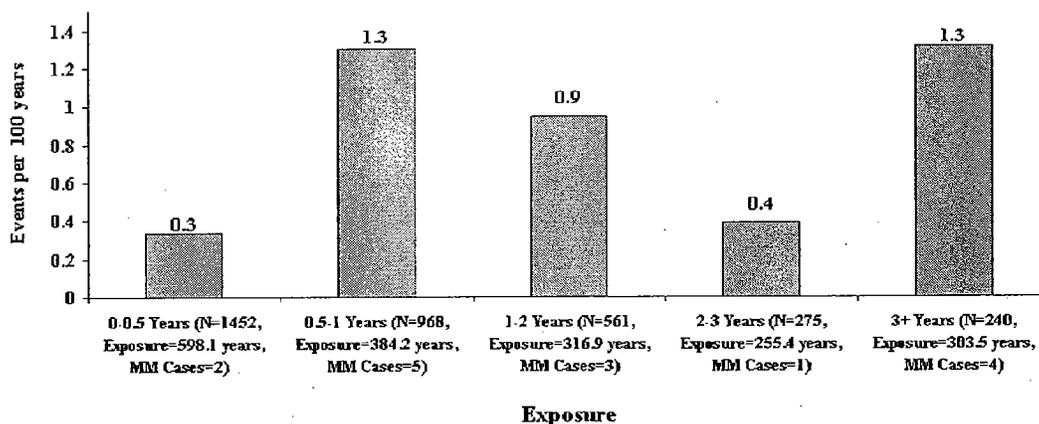
⁴ One additional case was identified in an ongoing trial subsequent to the submission of the safety update. The case of melanoma was diagnosed in subject #72, a 59 year-old man in the TEMPO Extension (233) study. He had received rasagiline since 11/6/1998, and the melanoma was biopsied on / after 1986 days of rasagiline exposure, or 66.2 months). He had been treated with rasagiline 1 mg/day.

Histologically, of the 16 melanomas associated with rasagiline treatment, seven were invasive and nine were in situ. The 15 rasagiline-treated participants with melanoma were exposed to rasagiline between 2.5 to 55 months (median 13 months, mean 21 months) prior to diagnosis.⁵ Seven of the 15 cases were identified within nine months of treatment. Five of the rasagiline-treated cases were dosed at 2 mg/day, eight received 1 mg/day and two received 0.5 mg/day. Eleven cases (those from PRESTO and LARGO) had concomitant treatment with levodopa.

It should be noted that only eight of the eleven melanoma patients that had concomitant treatment with levodopa were treated with rasagiline. Based on a simple proportion of patients who developed melanoma at the various doses, there did not seem to be a dose response relationship (0.5 mg 0.9% [2/232]; 1 mg 1.1 % [8/703]; 2 mg 1.2% [5/406]⁶). However, this calculation does not consider the actual person time at each dose. The person time totals were not presented in a way that allowed a dose response for melanoma rate to be easily calculated. We will ask the sponsor to do this calculation.

The following figure shows the rate of melanoma in the development program over time.

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



The rate of melanoma over time does not suggest a cumulative effect of rasagiline. Although the rates are calculated using person-time exposure, it should be noted when examining the above figure that the bars represent the exposure accumulated during varying epochs of time. The first two bars represent six months each, the third and fourth bars represent one year each, and the fifth bar represents 2-3 years of exposure.

If one were to compare the incidence of melanoma occurring only in the randomized controlled trials, the table below shows the rates observed.

⁵ Calculated by Dr. Jones from sponsor Table 3, NDA appendix 18.3, pg. 24

⁶ The denominator N=406 includes patients treated with 2 mg, as well as those started on 2 mg who later received 1 mg in the open label extension. The denominators for all dose groups were derived from FDA Table 9: Distribution of Cohort 9 (All PD Patients Exposed to Rasagiline) by Rasagiline Dose (Sponsor 120 Day Safety Update Table 4), p. 26 of Dr. Jones' review.

FDA Table 2. Rates of melanoma in placebo-controlled trials

	Rasagiline			Placebo		
	n	PY	Rate*	n	PY	Rate*
TEMPO	1	120.5	8.3	0	63	0
PRESTO	3	145.8	20.6	0	73.8	0
LARGO	0	77.2	0	1	73.6	13.6
Total	4	343.5	11.6	1	210.4	4.8

*rate per 1000 patient-years (PY)

The differences in melanoma rates between the rasagiline arms and the placebo arms were not statistically significantly different in each individual trial, or when all the trials were combined.

2.3.2.2 Sponsor's conclusions

Teva has concluded that the melanomas are not related to rasagiline treatment. Their conclusion is based on several arguments. They are summarized below.

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

2.3.2.3 Discussion of Sponsor's Arguments

In her review, Dr. Jones explores each of the sponsor's arguments in great detail. I will briefly address each point.

1. When comparing observed cases of melanoma in the rasagiline NDA safety experience to those expected for the population based on the rates measured by the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) Program, there is an excess observed in the rasagiline development

program because of underascertainment of melanoma (especially in situ) in the SEER database.

Dr. Jones contacted several member cancer registries that make up SEER to assess their methods for ascertaining melanoma cases. These registries replied that they have procedures in place for ascertaining cases from private pathology labs, in addition to hospital pathology labs, so that even if patients had their melanoma removed as an outpatient and sent to a private pathology lab, the case should still be detected by the member registry (although it may take a longer time to get entered into the registry).

Dr. Jones also reviewed the medical literature that has examined potential underreporting of melanoma to SEER. Across several studies, the high end of the range of underreporting of melanoma to SEER appears to be about 20%. It should be noted that although SEER collects invasive and in situ melanomas, it only reports rates of invasive melanomas.

The table below (excerpted from Dr. Jones' review) shows the observed to expected ratios for invasive melanomas associated with rasagiline treatment compared to what would be expected based on the background rate as measured by SEER.

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

Observed/Expected Analysis using SEER Rates		
8 Invasive Cases Observed (NDA Submission – Sept. 2003)		
Expected Number of Melanomas as per SEER rates	Obs/Exp Ratio	95% CI
0.9 cases	8.9	3.8, 17.5
1.13 (1.5 x SEER)	6.1	3.0, 13.9
1.8 cases (2 x SEER)	4.4	1.9, 8.7
2.7 cases (3 x SEER)	3.0	1.3, 5.8

As seen in the table above, even when underreporting is adjusted for by increasing the background rate three-fold (300%), the number of invasive melanomas observed in the rasagiline development program is still statistically significantly higher than what would be expected.

However, it should be noted that following the identification of the melanoma signal in 2001, regular screening with quarterly dermatological examinations was instituted in the ongoing rasagiline trials. Thus comparing a number of invasive melanomas detected through active screening to the incidence observed in a populational registry that does not employ active screening may not be a fair comparison. For reference, the following table is provided that shows the comparison of the observed melanoma incidence in the rasagiline development program to the expected number based on SEER using the two

invasive cases that were identified in association with rasagiline exposure prior to the initiation of regular dermatological screening.

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

Observed/Expected Analysis using SEER Rates			
2 Invasive Cases Observed (Melanoma Report – June 2001)			
Expected Number	Obs/Exp Ratio	P Value	95% CI
0.392	5.10	0.06	0.62,18.43
0.490 (1.25 x SEER)	4.08	0.09	0.49,14.74
0.588 (1.5 x SEER)	3.40	0.12	0.41,12.29
0.784 (2 x SEER)	2.55	0.19	0.31,9.22
1.176 (3 x SEER)	1.70	0.33	0.21,6.14

Although the observed number of melanoma cases substantially exceeds the expected number based on SEER, the excess was not statistically significant. Of note, the sponsor at the time counted only one of the two invasive melanomas as potentially related to rasagiline treatment as the other was identified 2.5 months into the trial and was reportedly a “suspicious lesion” prior to entry into the trial.⁷

2. The relative increase of melanoma cases observed in the rasagiline development program is related to the institution of regular dermatological screening examinations.

The sponsor suggests that the statistically significant excess of cases shown in the table above is attributable to increased screening. The institution of formal dermatological screening certainly could play a role in improving melanoma detection. In order to assess the potential effect of screening on melanoma incidence, Dr. Jones obtained the rates of melanoma broken down by age and sex from a community screening program conducted by the American Academy of Dermatology (AAD).

The table below, excerpted from Dr. Jones’ review, shows the observed to expected ratio for invasive and in situ melanoma for the rasagiline development program compared to the screened population from the AAD study. It should be noted that Dr. Jones’ included

⁷ Dr. Gan, the DNDP safety reviewer, did not accept the sponsor’s explanation and used two cases of melanoma in the calculation of the observed/expected ratio.

only melanoma cases that were identified following the institution of the regular dermatological screening.

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

Invasive Melanoma				In Situ Melanoma			
Number Observed *	Number Expected **	O/E Ratio	95% CI ***	Number Observed *	Number Expected **	O/E Ratio	95% CI ***
All screened cases comparison							
4	1.52	2.6	0.7, 6.7	6	0.59	10.2	3.7, 22.1
Only cases detected at first screen comparison							
2	1.52	1.3	0.2, 4.8	3	0.59	5.1	1.05, 14.9

In the “all screened cases” comparison, it can be seen that the number of invasive melanomas observed during melanoma screening in the rasagiline development program was not statistically different than that expected, based on comparison to the AAD screened population. However, the number of in situ melanomas did exceed what would have been expected based on the comparison to the AAD screened population. It should be noted that a strength of using this comparison group is that the methodology of the AAD screening population was to identify all suspicious lesions, such that in situ melanomas should not have been underascertained. At the same time, although this comparison to a screened population addresses the detection bias introduced by screening, the comparison population probably included only a small subset of Parkinson’s patients, another factor that may affect melanoma incidence. An additional limitation of this comparison is that it compares the number of melanoma cases detected over time (at multiple screenings) in the rasagiline development program to the number expected based on the detection of a tumor at a single screening, in essence comparing an expected number based on prevalence to an observed incidence detected over time.⁸ Thus the expected number may be inflated because patients had regular dermatological exams over time, increasing the opportunity to detect a tumor.

In order to address this last limitation, Dr. Jones asked the sponsor to identify patients whose melanoma was identified on the first screening exam. Two of the four invasive cases and three of the six in situ cases were detected on the first screening examination. As seen above in the “only cases detected at first screen” comparison, the excess of invasive cases observed compared to expected was less marked than in the “all screened cases” comparison and was not statistically significant. The number of in situ cases detected at the first screening was also diminished compared to the “all screened cases” comparison, however, the excess remained statistically significant.

⁸ Most of the patients in the AAD screening program were examined only once; however, about 20% of patients were screened twice.

- Some of the relative increase may also be due to an association between Parkinson's disease itself and melanoma, or confounders such as age, or smoking/socioeconomic status. The sponsor finds the case report literature suggesting a possible relation between levodopa therapy and melanoma unconvincing.

As Dr. Jones points out, the literature linking melanoma to levodopa therapy is based on case reports. No adequate epidemiological study or randomized trial has been done to clarify the relationship between levodopa therapy and melanoma.

As summarized in Dr. Jones' review (section 5.4.3.1.2), the sponsor tried to address the more general question of melanoma incidence in the PD population by conducting studies to assess the frequency and characteristics of skin cancers among PD patients, at all stages of the disease and treated with any anti-Parkinson's therapy (except rasagiline). Interim analyses of the two studies (one in Israel and one in North America) suggest some increase in melanoma incidence in the PD population compared with the general population.

When the melanoma association with rasagiline first arose back in 2001, the Division at that time sent a data request to each of the approved therapies for PD asking for data on melanomas identified during the drug development programs and the person-time exposure accumulated during the development programs. As part of the rasagiline NDA safety review, Dr. Jones went back to the responses from the various sponsors and calculated the melanoma incidence for each of the development programs.

The table below, combined from tables 64 and 65 in Dr. Jones' review, summarizes the melanoma incidence in each of the PD drug development programs.

FDA Table 64: Summary of melanoma occurrence in PD therapy development programs

Sponsor	Principle Medication In Studies*	Total Subjects	Total PYs	% of Subjects from trials in NA only	Mel. Cases	% (Case/Pts)	Incidence Density per 1000 PYs
Orion	Entacapone	2202	2486	18	0	N/A	N/A
GSK	Ropinirole	3138	3377	22	1	0.031	0.3
Pharmacia	Pramipexole	5881	6909	37	11	0.19	1.6
Hoffman-LaRouche	Tolcapone	2847	3200	53	33	1.16	10.3
<i>Teva</i>	<i>Rasagiline</i>	<i>1935**</i>	<i>2450**</i>	<i>56</i>	<i>20</i>	<i>1.03</i>	<i>8.2</i>

As can be seen in the table above, there is a range of melanoma incidences across the PD drug development programs from zero (entacapone) to 10.3/ 1000 PYs (tolcapone), with rasagiline being at the high end of the range. Interestingly, the rates of melanoma vary with the proportion of subjects participating in North American trials. This pattern might correlate with the increased susceptibility of North American subjects to melanoma. But it also might correlate with the tendency of North American trials to report higher rates of

AEs than non-North American trials. In her review, Dr. Jones describes this finding from the rasagiline development program at length (see section 2.1.2 above). When comparing the AE rates from PRESTO (North American) to LARGO (non-North American), common AEs as well as serious AEs reported about twice as often (observed in both rasagiline and placebo groups).

4. The higher rate of melanoma in North American subjects is consistent with this population having more melanoma risk factors than European subjects.

Based on the sponsor's assessment of melanoma risk factors in rasagiline treated patients conducted just prior to the introduction of dermatological screening exams, participants in the North-American studies (133/135 PRESTO and PRESTO extension, 233 TEMPO extension) had more melanoma risk factors than those participating in the non-North-American studies (122/123 LARGO and LARGO extension). The table below shows the distribution of melanoma risk factors among the various trial participants.

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

Table 6. The percent of patients having multiple risk factors

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

As noted above in the discussion of point 3, the higher rate of melanoma in North American subjects is also consistent with better adverse event reporting in this population as compared to European subjects. The relative effect of these two potential confounders (e.g. more melanoma risk factors and better AE reporting) on melanoma incidence is unclear.

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

This contention by the sponsor is theoretical. Typically, one associates drug-related cancer risk with a certain time lag required for the drug to induce or promote a cancer. In the case of rasagiline (see figure above in section 2.3.2.1), the rate of melanoma over time does not suggest a cumulative effect of rasagiline. The early occurring cases also runs counter to the usual thinking about the latency required for cancer to occur.

It is certainly possible that early occurring melanomas may have been present at entry into the study and just not detected until after study commencement. However, the unanswered question is whether rasagiline could have a promoting effect on precancerous skin lesions that were already present.

Discussion with Dr. Paul Roney, pharmacology-toxicology reviewer for the rasagiline NDA, indicates that the genotoxicity battery suggests that rasagiline is a clastogen. Additionally, in carcinogenicity studies in mice, there was an increased incidence of combined lung adenoma/carcinomas (statistically significant only in male mice, but the trend was present in female mice). The histopathology was not complete in the rat study, so no conclusions can be made at this point regarding carcinogenicity in the rat.

Given the preclinical findings, it seems premature to conclude that inadequate latency is a strong argument against the possibility of melanoma being related to rasagiline.

2.3.2.4 Safety Team Proposal

2.3.2.4.1 Large Simple Trial

Dr. Jones concludes that although not every piece of evidence supports a relationship between rasagiline and melanoma, the excess rate of invasive melanoma in the rasagiline development program compared to the SEER database (even when corrected for underreporting) and excess rate of in situ melanoma in the rasagiline development program compared to the AAD screened database leads to uncertainty about the nature of the relationship. I agree that additional information is needed to better understand the potential relationship between rasagiline exposure and development of melanoma.

Dr. Jones suggests a randomized controlled trial conducted in the postmarketing period to address this unresolved safety issue. Often such studies are referred to as “large, simple trials (LST)”. The benefit of a LST is that many patients can be followed at a relatively low cost because minimal data is collected over the course of the trial. One difference from the usual LST in the proposed trial, however, is the conduct of regular dermatological examinations to increase the ascertainment of melanoma cases. This serves to protect patients in that if there is a real risk of melanoma associated with rasagiline treatment, the tumors would be detected at an early stage. Patients would also require a thorough baseline dermatological examination so that anyone with preexisting lesions would be identified and excluded. Important covariates regarding melanoma risk factors would need to be collected as well so that they could be controlled for in the analysis of the data. Additionally, it would be beneficial to stratify patients by monotherapy and adjunctive therapy so that factors related to duration of PD would be similar. Discussions with the sponsor about trial design will have to include consideration of duration of study, sample size, and comparison group.

Additionally, consideration should be given to conducting the LST prior to approval. This would be particularly appropriate if the clinical team were to determine that rasagiline does not add any unique efficacy benefits to the armamentarium of Parkinson’s disease therapies.

2.3.2.4.2 Proposed Melanoma Labeling

The general approach of the safety team has been to include a given adverse event in the Precautions or Warnings section when there is reliable data suggesting that the drug is a causative factor in that adverse event.

Although there is some data suggesting a potential role for rasagiline in causing melanoma (e.g., the comparison of those whose melanomas were detected after the first screening to the expected based on the AAD screening program), there is other data that is not as supportive (e.g., evidence that melanoma is increased in Parkinson's disease patients as a group). Thus the evidence for a causative relationship is not as robust as we often like to see to support a Precautions or Warnings statement.

Nevertheless, given the potentially severe sequelae of an undiagnosed melanoma, Dr. Jones has proposed a  should rasagiline be recommended for approval. The proposed language that follows is adapted from her proposal.


Melanoma



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/s/

Judith Racoosin
6/25/04 12:42:16 PM
MEDICAL OFFICER

Correction to NDA Safety Review

NDA: 21-641

Drug Name: Generic Name: Rasagiline
Proposed Trade Name: Agilect ®

Sponsor: Teva Neuroscience, Inc.

Action Date: July 5, 2004

Reviewer: M. Lisa Jones, MD, MPH

Subject: Revision of the Rasagiline Safety Review: Reduction of Melanoma Cases within the Tolcapone Development Program

Material reviewed: 6/28/04 email response to 6/18/04 teleconference questions

1. Overview

As part of the analysis of melanoma within the rasagiline development program, datasets summarizing melanoma occurrence within other Parkinson's disease development programs were solicited from their respective sponsors. Shortly after the rasagiline safety review was completed, one of the sponsors who had sent such a dataset (Hoffman-La Roche/tolcapone) reported that the number of melanoma cases within their originally submitted dataset was incorrect: there were in fact only four verifiable cases of melanoma, instead of the initially stated 33 cases.

The following erratum updates the relevant tables and text within the rasagiline safety review, and should be considered to replace these sections.

2. Clarification of Melanoma Cases Occurring within the Tolcapone Development Program

As described in Section 5.5.4 of the rasagiline safety review, in order to assemble a comparator group for the analysis of melanoma within the rasagiline development programs, datasets summarizing melanomas occurring within other Parkinson's disease therapy development programs were requested from the respective sponsors. The dataset submitted by Hoffman-La Roche for the tolcapone development program indicated that there were 33 cases of melanoma. As this number of melanomas was considerably higher than that of other Parkinson's disease development programs, and as this number was also substantially higher than the number of melanomas previously reported by Hoffman-La Roche for the tolcapone development program, the Division of

Neuropharmacological Drug Products (DNBP) requested clarification of the number of melanoma cases from the sponsor during a teleconference on June 18, 2004.

On June 28, 2004, the sponsor replied by e-mail that they had reviewed the 33 cases reported in the dataset, and found that only four could be confirmed as melanomas. The remaining cases were non-melanoma skin cancers, although in one case neither a melanoma nor a non-melanoma skin cancer had been recorded for the subject.

3. Updated Analysis Results Based on the Reduction in Melanoma Cases

3.1 Updated Tables Based on Reduction in Melanoma Cases

The analyses in Section 5.5.4 of the rasagiline safety review utilized the 33 cases initially reported within the tolcapone development program dataset. As the sponsor has since reported that there were in fact only four melanomas during the tolcapone development program, the following two analyses tables were revised. The revisions are shown in **bold, underlined** text within the tables.

FDA Table 66: Summary of melanoma occurrence in PD therapy development programs (From pg. 132 of the rasagiline safety review)

Sponsor	Principle Medication In Studies*	Total Subjects	Total PYs	Mel. Cases	% (Case/Pts)	Incidence Density per 1000 PYs
Lilly	Pergolide	942	930	0	N/A	N/A
Pharmacia	Pramipexole	5881	6909	11	0.19	1.6
GSK	Ropinirole	3138	3377	1	0.031	0.3
Orion	Entacapone	2202	2486	0	N/A	N/A
Hoffman-La Roche	Tolcapone	2847	3200	<u>4</u>	<u>0.14</u>	<u>1.25</u>
Teva	<i>Rasagiline</i>	<i>1935**</i>	<i>2450**</i>	<i>20</i>	<i>1.03</i>	<i>8.2</i>

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

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

**120-day safety update, Section 2.1.1

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

(From pg. 132 of the rasagiline safety review)

Development Program	RCTs in North America/Total [# Trials (Pts.)]	Extension Trials in North Amer./Total [# Trials (Pts.)]	% of Subjects from Trials in North America Only	Melanoma Incidence Density per 1000 PYs
Entacapone	1(205)/5(1303)	2(194)/6(899)	18	N/A*
Ropinirole	3(515)/13(2238)	2(123)/9(710)	22	0.3
Pramipexole	8(1534) /19(3771)	4(938)/13(2874)	37	1.6

Tolcapone	4(876)/8(1450)	4(625)/9(1397)	53	1.25
Rasagiline	2(876)/3(1563)	2(644)/3(1124)	56	8.2
Pergolide	**	**	**	**

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

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

In addition, Table 3 in Appendix 9.2.7 of the rasagiline safety review lists the 33 cases incorrectly identified by the tolcapone development program dataset. This should be reduced to the four cases that were verified by the sponsor. The corrected table is given below:

Table 3. Characteristics of melanoma cases during tolcapone clinical development
(From pg. 210 of the rasagiline safety review)

Patient ID #	Age/ Sex	Trial ID #	Study Location	Tx Group (RCT/Ext.)	Levo -dopa?	Days to dx*	Dx'ed RCT or Ext?
12848/0202	70/M	14316	North America	Placebo/Tolc.	Yes	574*	Ext.
15301/0200	53/F	14657	Non-North America	Tolcapone/Tolcapone	Yes	187*	Ext.
15393/0516	68/M	14657	Non-North America	Tolcapone/Tolc	Yes	470*	Ext.
15937/0307	74/M	14971	North America	Tolcapone/Tolc	Yes	312*	Ext.

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

3.2 Updated Text Based on Reduction in Melanoma Cases

The following text sections within the rasagiline safety review were also affected by the reduction of melanoma cases:

- 1. Change of Rasagiline Development Program from Second Highest to Highest Melanoma Rate Among the Parkinson's Disease Therapy Development Programs (Executive Summary pg. 6, Melanoma Data Analysis pg. 131-132, Melanoma Conclusions pg. 134, Discussion pg. 152):** These sections state that the rate of melanoma in the rasagiline development program was exceeded by the tolcapone development program. When the revised number of four melanoma cases within the tolcapone development program is used in the analyses, the development program with the highest rate of melanoma is the rasagiline development program, followed by pramipexole with the second highest rate, and tolcapone with the third highest rate (Revised FDA Table 66 above).
- 2. Reduction in the Correlation of Melanoma Rate with Percentage of Subjects from North America (Melanoma Data Analysis pg. 133):** The text following the Table 67 of the rasagiline safety review concludes that the rate of melanoma within the various development programs correlates with the percent of North American subjects within the development program. When the rate of melanomas within the

tolcapone is revised to reflect four cases of melanoma instead of 33, this correlation is significantly reduced to the point that the trend is not apparent (revised FDA table 67 above).

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/s/

M. Lisa Jones
7/26/04 10:08:07 AM
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Judith Racoosin
7/26/04 01:50:57 PM
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NDA Safety Review

NDA: 21-641

Drug Name: Generic Name: Rasagiline
Proposed Trade Name: Agilect ®

Sponsor: Teva Neuroscience, Inc.

Action Date: July 5, 2004

Reviewer: M. Lisa Jones, MD, MPH

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The Executive Summary – Safety Review	5
1. Materials Used in This Review	11
2. Background	11
2.1 Name, Drug Class, Proposed Indication	11
2.2 State of Armamentarium- Safety	12
2.3 Proposed Rasagiline Labeling with Respect to Safety	12
2.4 Animal Pharmacology and Toxicology	16
2.5 Human Pharmacokinetics	17
3. Approach to Safety Review/Methods	18
4. Review Findings	18
4.1 Description of Data Source	18
4.1.1 <i>Overview of Trials</i>	18
4.1.2 <i>Summary of Pivotal Trials</i>	19
4.1.3 <i>Sponsor Analysis Cohorts</i>	21
4.2 Summary of Exposure	24
4.2.1 <i>Number of Subjects</i>	24
4.2.2 <i>Exposure by Duration</i>	26
4.2.3 <i>Exposure by Dose and Duration</i>	26
4.2.4 <i>Exposure by Age</i>	27
4.2.5 <i>Exposure by Sex</i>	28
4.3 Review of AE Surveillance and Coding of AEs	28
4.4 Audit Findings and Evaluation of the AE Coding	32
4.5 Clinical Pharmacology Studies: Safety	33
4.5.1 <i>Clinical Pharmacology: Exposure</i>	34
4.5.2 <i>Clinical Pharmacology: Mortality</i>	35
4.5.3 <i>Clinical Pharmacology: Serious Adverse Events</i>	35
4.5.4 <i>Clinical Pharmacology: Discontinuations for Adverse Events</i>	36
4.5.5 <i>Clinical Pharmacology: Treatment Emergent Adverse Events</i>	37
4.5.6 <i>Clinical Pharmacology: Laboratory Data</i>	39
4.5.7 <i>Clinical Pharmacology: Vital Sign Data</i>	40
4.5.8 <i>Clinical Pharmacology: ECG Data</i>	40
4.6 Phase II/III Studies	41
4.6.1 <i>Deaths</i>	41
4.6.2 <i>Serious Adverse Events</i>	46
4.6.3 <i>Discontinuation for Adverse Events</i>	55
4.6.4 <i>Common Adverse Events</i>	65
4.6.5 <i>Laboratory Data</i>	78
4.6.6 <i>Vital Signs</i>	85
4.6.7 <i>ECG data</i>	93
4.7 Drug Demographic Interactions	99
4.7.1 <i>Sex</i>	99
4.7.2 <i>Age</i>	100
4.8 Drug-Drug Interaction	102

4.8.1 Concomitant Dopamine Agonists	102
4.8.2 Concomitant Entacapone	102
4.8.3 Concomitant Amantadine.....	102
4.8.4 Concomitant Antidepressants	103
4.8.5 Concomitant CYP 1A2 Inhibitors or Substrates	103
4.9 Overdose	103
4.10 Withdrawal.....	104
4.11 Drug Disease Interaction.....	104
5.0 Special Safety Issue: Melanoma	104
5.1 Materials Reviewed	104
5.2 Introduction.....	105
5.2.1 Background Timeline	105
5.2.2 Prior FDA Review.....	107
5.3 Sponsor Presentation of Data.....	110
5.3.1 Melanoma Case Characteristics.....	110
5.3.2 Overview of Sponsor Position.....	111
5.4 Discussion of Specific Sponsor Concerns	112
5.4.1 Sponsor Concern: Incomplete Melanoma Ascertainment in SEER.....	112
5.4.2 Sponsor Concern: Surveillance Bias following Screening	116
5.4.3 Sponsor Concern: Confounding by Medications or Parkinson's disease	120
5.4.4 Sponsor Concern: Increasing Melanoma Rates Worldwide.....	124
5.4.5 Sponsor Concern: Insufficient Latency.....	124
5.4.6 Sponsor Concern: Differential Exposure to Rasagiline versus Placebo	126
5.5 Ongoing FDA Review	127
5.5.1 Comparison Group Overview.....	127
5.5.2 SEER Data as the Comparator Group.....	127
5.5.3 AAD Screening Data as Comparator Group	128
5.5.4 Data from other Parkinson's Disease Therapy Development Programs	131
5.5.5 Placebo-Controlled Portions of TEMPO, LARGO and PRESTO	133
5.5.6 Logistic Regression	134
5.6 Conclusions.....	134
5.6.1 Phase IV Randomized Controlled Trial.....	135
6. Review of Systems.....	135
6.1 Cardiovascular (CV)	136
6.2 Gastrointestinal (GI)	138
6.3 Central and Peripheral Nervous System (CPNS).....	139
6.4 Psychiatric.....	140
6.5 Respiratory.....	141
6.6 Musculoskeletal (MS).....	142
6.7 Metabolic and Nutritional (MN).....	143
6.8 Urological Reproductive (UR).....	144
6.9 Skin and Appendages.....	145
6.10 Vascular	146
6.11 Hematological and Lymphatic System	147
6.12 Special Senses Disorders	148
6.13 Endocrine	149

6.14 Body as a Whole	149
7. Discussion	150
8. Edited Rasagiline Proposed Labeling	157
9. Attachments	172
9.1 Summary of Studies in the Rasagiline NDA	172
9.2 Summaries of Death Narratives for Rasagiline-Treated Participants	177
9.3 Serious Adverse Events in Cohort 2	185
9.4 Serious Adverse Events in Cohort 9	187
9.5 Adverse Events Associated with Early Termination in Cohort 2	191
9.6 Adverse Events associated with Early Termination for all Participants Exposed to Rasagiline.....	192
9.7 Laboratory Normal and Potentially Clinically Significant Limits.....	195
9.8 Number and Percent of Subjects with Shifts from Low/Normal to High and High/Normal to Low from Cohort 1 Biochemistry Results.....	196
9.9 Number and Percent of Subjects with Shifts from Low/Normal to High and High/Normal to Low from Cohort 2 Biochemistry Results.....	196
9.10 Narratives for Selected Cohort 2 Participants with PCS Biochemistry Lab Changes.....	196
9.11 Narratives for Selected Cohort 2 Participants with PCS Biochemistry Lab Changes.....	197
9.12 Number and Frequency of Shifts from Low/Normal to High and High/Normal to Low from Cohort 1 Hematology Results.....	198
9.13 Narratives of Selected Cohort 1 Participants with Hematological PCS Results	198
9.14 Number and Frequency of Shifts from Low/Normal to High and High/Normal to Low for Cohort 2 Hematology Results.....	200
9.15 Shift Analysis for Urinalysis from Baseline to LOV for TEMPO, LARGO and PRESTO.....	200
9.16 Number and Percent of Cohort 2 Subjects Reporting AEs by Dopamine Agonist Use	201
9.17 Number and Percent of Cohort 2 Subjects Reporting AEs by Entacapone Use.	202
9.18 Number and Percent of Cohort 2 Subjects Reporting AEs by Amantadine Use	202
9.19 Number and Percent of Cohort 2 Subjects Reporting AEs by Antidepressant Use	203
9.20 Number and Percent of Cohort 2 Subjects Reporting AEs by SSRI Use	203
9.21 Concomitant use of Anxiolytic, Sedative, Hypnotic and Neuroleptic Agents in LARGO and PRESTO	204
9.22 Summary of Melanoma Cases	204
9.23 Information from SEER Registries on in situ Melanoma	205
9.24 Summary of Published Case Reports of Melanoma with Levodopa Usage	206
9.25 Age-Adjusted Background Melanoma Rates by Country for Clinical Sites from TEMPO, LARGO and PRESTO.....	206
9.26 Calculations of Melanoma Rates in other Parkinson's Disease Therapy Trials .	208
9.27 Construction of the Post-Screening Rasagiline Dataset.....	211
9.28 Biopsy-Confirmed Melanomas Among all Persons Screened for the American Academy of Dermatology Screening Program, 1992-1994.....	213
9.29 Sources of Sponsor Data Presented Within the Review of Systems (ROS).....	214

The Executive Summary – Safety Review

Introduction

Rasagiline is an orally-administered, selective MAO-B inhibitor that has not been previously marketed outside the United States. Teva is seeking FDA approval to market rasagiline for the treatment of Parkinson's disease (PD), both as monotherapy and as an adjunct to levodopa. Selegiline, another MAO-B inhibitor, has been approved for the treatment of Parkinson's disease in the United States since 1989. Other approved Parkinson's disease therapies include the dopamine agonists, COMT inhibitors, anticholinergics and amantadine.

Safety Data Sources

The rasagiline development program included primary safety data from three Phase III placebo-controlled trials:

- **TEMPO:** Rasagiline monotherapy in early PD patients in North America. This 26 week study included three treatment arms: rasagiline 1mg/day (n=134), rasagiline 2 mg/day (n=132) and placebo (n=138).
- **PRESTO:** Rasagiline as an adjunct to levodopa in more advanced PD patients in North America. This 26 week study included three treatment arms: rasagiline 0.5 mg/day (n=164), rasagiline 1 mg/day (n=149) and placebo (n=159).
- **LARGO:** Rasagiline as an adjunct to levodopa in more advanced PD patients in Europe, Argentina and Israel. This 18 week study included three treatment arms: rasagiline 1 mg/day (n=231), entacapone (n=227) and placebo (n=229).

Each placebo-controlled trial was followed by a blinded, active control (different dosages of rasagiline) phase and subsequently an open label extension.

Safety data was also submitted for fifteen Phase I/II studies. A total of 1537 participants were exposed to rasagiline at any dose, which just meets the ICH guidelines for exposure to a chronically administered drug product¹. The number of subjects exposed to the indicated dose (1 mg/day) at six months and one year also met ICH guidelines.

For the safety analysis, Teva divided participants in the rasagiline development program into nine cohorts², including Cohort 1 (placebo-controlled rasagiline monotherapy), Cohort 2 (placebo-controlled rasagiline as levodopa adjunct) and Cohort 9 (all PD patients exposed to rasagiline).

Deaths

A total of twenty-one rasagiline-treated subjects, five entacapone-treated subjects and six placebo-treated subjects died during the rasagiline development program. The reported causes of death were those expected in an older population. Six rasagiline-treated

¹ The ICH guidelines for exposure to a chronically administered drug product recommend that at least 1500 patients are exposed to the drug, with 300 receiving treatment for six months and 100 receiving treatment for one year.

² See section 4.1.3 Sponsor Analysis Cohorts for the details of each cohort membership.

subjects, compared to no placebo or entacapone-treated subjects, died of cerebrovascular accidents. However, rates of non-fatal cerebrovascular accidents were similar between the rasagiline and placebo treatment groups in the two placebo-controlled cohorts.

Serious Adverse Events (SAEs)

In general, rasagiline and placebo subjects had similar SAE risks. In the primary data trials, there were no SAEs of liver failure, acute renal failure, aplastic anemia, serious skin reactions, or pancreatitis. Two SAEs of rhabdomyolysis were reported in ongoing studies, both following a fall and prolonged immobilization. One case lacked laboratory values (creatinine phosphokinase) verifying rhabdomyolysis.

Seventeen cases of melanoma were diagnosed among fifteen rasagiline-treated subjects (one patient had two lesions) and one placebo-treated subject. Three subjects were diagnosed with melanoma before treatment initiation. One rasagiline-treated subject died due to melanoma. A number of factors complicated the analysis of melanoma within the rasagiline development program. The most significant of these were that most of the cases were diagnosed in extension trials lacking concurrent controls, and that the majority (14 of 20) were identified following the implementation of regularly scheduled skin examinations in all rasagiline clinical trials. Other confounding factors include older age, the presence of concomitant Parkinson's disease and medications (especially levodopa), the variable melanoma risk factors and background rates for the geographic locations of the study sites, and rapidly increasing rates of melanoma worldwide.

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

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

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

Discontinuations

Overall, 9.4% of rasagiline-treated subjects discontinued the development program early due to adverse event. In the placebo-controlled monotherapy cohort, the rate of discontinuation was higher in rasagiline-treated subjects (7.8/100 PYs) than in placebo subjects (1.5/100 PYs). In the placebo-controlled monotherapy cohort, the most frequently reported AE leading to discontinuation in rasagiline subjects was hallucinations (1.3% [n=2] rasagiline 1 mg; 0% placebo), followed by flu syndrome, chest pain, hypertension, chest pain and urinary tract infection (each reported by one rasagiline-treated subjects.)

In the placebo-controlled rasagiline as levodopa adjunct cohort, rasagiline subjects (11/100 PYs) and placebo subjects (13/100 PYs) discontinued early due to AE at a similar rate. AEs reported for more than one discontinuing rasagiline-treated subjects, and which were more frequent than in placebo subjects, were hallucinations, postural hypotension, abdominal pain and dyspnea.

Adverse Events

The safety testing, capture of adverse events, coding of investigator terms and analyses of safety data were generally adequate, with the exceptions noted below. The safety data were essentially consistent across the submitted case report forms, electronic data sets, and summary tables. After reviewing the adverse events coding dictionary, this reviewer requested that the sponsor recode several verbatim terms to more appropriate preferred terms. The most notable of these was that fall-related adverse event verbatim terms be coded to both a new preferred term (PT) "FALLS" and, when fall-related verbatim terms included two or more events, to a reasonable PT for the precipitant or resultant verbatim term.³

Following the re-coding described above, the most common adverse events (defined by the sponsor as those occurring in 2% or more of the rasagiline 1 mg group and numerically at least twice as frequent than in the placebo group) for rasagiline monotherapy were⁴ flu syndrome, depression, rhinitis, conjunctivitis, fever, malaise, neck pain, neoplasm, arthritis, vertigo, ecchymosis, gastroenteritis, and infection. The most common adverse events for rasagiline as levodopa adjunct were postural hypotension, accidental injury, constipation, weight loss, abdominal pain, vomiting, dystonia, anorexia and abnormal dreams.

No consistent pattern in the occurrence of adverse events was observed for age or gender. Rasagiline-treated subjects who received concomitant dopamine agonists had an elevated rate of several adverse events compared to those who did not receive concomitant dopamine agonists, including extrapyramidal syndrome, skin disorders and hallucinations. There were no occurrences of rasagiline overdose and no pregnancies in patients taking rasagiline reported during the clinical development program.

³ For example, a verbatim term such as "fall resulting in wrist fracture" would be coded to the preferred terms "FALL" and "ACCIDENTAL INJURY"

⁴ The most common AEs for both rasagiline monotherapy and rasagiline as levodopa adjunct given in this section of the review are listed in order of descending percentage of rasagiline-treated subjects.

Vital Signs and Laboratory Data

During vital sign monitoring, postural hypotension was observed in a higher percentage of rasagiline-treated subjects than placebo subjects, especially in the levodopa adjunct cohort (rasagiline 3.2%, placebo 1.3%). In addition, postural hypotension was reported as an adverse event by 4.7% of rasagiline-treated subjects in Cohort 2, compared to 1.3% of placebo-treated subjects.

With the exception of postural hypotension, no important differences in vital sign or laboratory data were observed between the rasagiline and placebo treatment groups.

ECG

Teva's analyses of ECGs did not suggest rasagiline-related QT prolongation compared to placebo. However, the data presented for rasagiline monotherapy (Cohort 1) was severely limited, particularly in comparison to that provided for subjects receiving rasagiline as levodopa adjunct (Cohort 2).

Special Studies: Tyramine

Teva conducted an assessment of the effect of co-administration of rasagiline and tyramine-containing foods to determine whether there is a "cheese effect" (tyramine-induced hypertensive crisis.) A review of these studies are included in Dr. Len Kapcala's review of rasagiline efficacy.

Recommendations

Additional Analyses

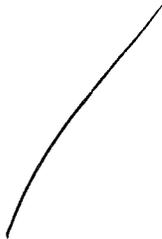
- Although much of the data accumulated during the rasagiline development program is not supportive of a causal association between rasagiline and melanoma, other analyses do suggest an elevated risk. However, these analyses are limited by the lack of a parallel control group with comparable demographics and Parkinson's disease history. It is therefore recommended that the Division request a Phase IV commitment wherein Teva conducts a randomized controlled trial of melanoma rates in Parkinson's disease patients who are exposed or not exposed to rasagiline.
- The ECG data for Cohort 1 subjects and for Phase I/II subjects is limited to the extent that it is insufficient to allow conclusions regarding the cardiac effects of rasagiline monotherapy. The sponsor states that because ECG analysis in the Cohort 1 study TEMPO consisted solely of classifying ECGs as normal or abnormal (without collecting data on the nature of the abnormality or measuring of ECG intervals), additional data is not immediately available. It is presumed that the sponsor has retained the original ECG tracings from TEMPO, and it is recommended that these be re-read in a method similar to the sponsor analysis of ECG data for the levodopa adjunct studies. This may include having the ECGs assessed by a centralized facility and more detailed assessment of the QT interval.

- The sponsor stated that in approximately 7% of discontinuations they were unable to attribute the discontinuation to a particular AE. In such cases they did not include the AE data for that subject in the data tables for discontinuations, although they did discuss these discontinuing subjects in the corresponding text sections of the NDA. The sponsor should take additional measures to identify the AEs associated with discontinuation. This may include evaluating a listing of all AEs reported by discontinuing subjects along with the dates of their AEs and discontinuation.
- There is a substantial excess of flu-syndrome, arthralgia and fever in rasagiline-treated subjects compared to placebo, most notably in the rasagiline monotherapy cohort (In cohort 1, 4.7%⁵ of rasagiline-treated subjects reported flu syndrome, compared to 0.7% in placebo-treated subjects: a 6.7-fold excess in the rasagiline treatment group.) Within the NDA the sponsor does not provide analysis or commentary on this potential safety signal beyond describing its occurrence. The sponsor should present additional analysis exploring the nature of this potential syndrome. These analyses may include the following: creation of a case definition, reassessment of verbatim adverse events to ascertain which meet the case definition, trends in associations with other adverse events, concomitant medication (especially amantadine) and examination of these adverse events over time.

Recommendations for the Proposed Labeling

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

Melanoma



⁵ The 4.7% flu syndrome in rasagiline-treated subjects represents the percent following the FDA-requested revision of the coding of certain verbatim terms, and was submitted with the 120 Day Safety Update. In the initial NDA submission, 6.0% of rasagiline-treated Cohort 1 subjects were reported flu syndrome, but a number of these were cases of gastroenteritis inappropriately classified as flu from the verbatim term "stomach flu."

For the subjects treated with rasagiline, median duration of treatment until melanoma diagnosis was 13 months (mean 21 months), with a range of 2.5 to 55 months. Nine of the melanomas in rasagiline-treated subjects were from the North American monotherapy study TEMPO, and seven of the melanomas in rasagiline-treated subjects were from the levodopa adjunct study PRESTO.

A potential causal relationship between rasagiline treatment and melanomas is being evaluated. Until the risk associated with rasagiline is better understood, patients and providers are advised to monitor for melanomas as appropriate for the patient's melanoma risk factor profile.

- This reviewer requested that some preferred terms within the initially submitted AE Coding Dictionary be re-coded. As a result of this re-coding there was some shifting of preferred terms meeting or not meeting criteria for “common” and “most common” AEs. Specifically, for the rasagiline monotherapy placebo-controlled cohort, the new preferred term “Falls” meets the criteria for common AEs, while ecchymosis, gastroenteritis, and infection would meet criteria for “most common.” In the placebo-controlled rasagiline as levodopa adjunct cohort, ecchymosis, falls and colds were classified as common AEs, while accidental injury was reclassified from “common” to “most common” and arthralgia from “most common” to “common.” The tables of treatment emergent AEs in the proposed labeling should be revised to reflect these changes.
- There was a significantly higher rate of AE reporting in the levodopa adjunct North American study PRESTO (in which 90% of subjects reported AEs) than in the Non-North American study LARGO (in which 50% of subjects reported AEs). Although this discrepancy in AEs was somewhat less when only serious adverse events were compared, it nevertheless remained. The sponsor suggests these differences may be due to cultural variation, however it would seem that serious adverse events should not be greatly influenced by potential cultural differences among study populations.

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

- Postural hypotension was a common adverse event, especially when rasagiline was used as an adjunct to levodopa. A statement noting this should be made prominent within the labeling.
- In the proposed labeling Teva notes that significant adverse events have been reported with the use of MAO inhibitors and various concomitant medications. In contrast to the selegiline labeling, the rasagiline proposed labeling does not state specifically what these events were. More detailed information on the nature of

the significant adverse events referred to in the rasagiline proposed labeling should be provided.

- The sponsor statements regarding concomitant use of antidepressants and rasagiline during the development program should specifically acknowledge the restrictions on antidepressant usage within the trials and the exact number of subjects to whom rasagiline and antidepressants were co-administered.
- Although overdose has not yet been observed with rasagiline, based upon experience with other selective MAO inhibitors more specific information on the expected symptoms and general treatment should be provided

1. Materials Used in This Review

This safety review is based upon information contained in the following sponsor documents:

- NDA Electronic Integrated Summary of Safety (ISS) including post-text tables, electronic datasets, electronic case report forms (CRFs), and appendices; dated August 2003
- NDA Electronic Clinical Overview; dated August 2003
- NDA Electronic Non-Clinical Overview; dated August 2003
- NDA Electronic Study Reports for Trials TEMPO (TVP-1012/232), PRESTO (TVP-1012/133) and LARGO (TVP-1012/122), including their respective extension studies; dated July – August 2003
- NDA Electronic Revised AE Coding Dictionary; dated December 2003
- NDA Electronic 120-Day Safety Update, including ISS with post-text table; dated December 2003
- Electronic Integrated Summary of Safety: Phase I and II Clinical Pharmacology Studies; dated March 2004
- E-mail Communications to Teva Representative on 10/22/2003, 11/10/2003, 12/11/2003, 1/5/2004, 1/17/2004, 2/2/2004, 3/6/2004, 3/15/2004, 4/16/2004 and 4/19/2004

Other sponsor and prior DNDP documents utilized in the review of melanoma within the rasagiline development program are listed in Section 5.0 (Special Safety Issues – Melanoma) of this review.

2. Background

2.1 Name, Drug Class, Proposed Indication

Rasagiline (1H-Inden-1-amine, 2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate) is an irreversible monoamine oxidase inhibitor, selective for the B form of the enzyme (MAO-B). It is administered orally. Preclinical studies suggest rasagiline may elevate extracellular striatal dopamine levels (Nonclinical Overview 2.4.2.1). The sponsor, Teva Pharmaceutical Industries, seeks FDA approval to market rasagiline for the treatment of patients with idiopathic Parkinson's disease, as either monotherapy or as an adjunct to levodopa.

Rasagiline has not been previously marketed outside of the United States.

2.2 State of Armamentarium- Safety

Selegiline, another MAO-B inhibitor, has been approved in the United States for treatment of Parkinson's disease since 1989. Safety considerations noted in the selegiline labeling include: contraindication with meperidine use, warnings with co-administration of tricyclic antidepressants or SSRI's, and exacerbation of levodopa side effects. The most common adverse events (AEs) leading to drug discontinuation in pre-marketing clinical trials were nausea, CNS effects (including hallucinations), loss of balance, insomnia and orthostatic hypotension.

In the postmarketing period, rare cases of hypertensive reaction to tyramine have been reported with selegiline use, even within the recommended dose range. This is noted in the selegiline labeling, which also states that dietary restrictions are not ordinarily required. A case of pseudo-pheochromocytoma has been attributed to an interaction of selegiline, ephedrine and a tricyclic antidepressant (Clin Endocrinol 1995. 42(1):95-98).

The principle Parkinson's disease therapy is levodopa, typically administered with a decarboxylase inhibitor such as carbidopa. With prolonged use, increasing motor complications may occur. Other common adverse events associated with levodopa use include orthostatic hypotension, nausea, vomiting, and psychiatric disturbances. Table 1 summarizes additional classes of Parkinson's disease therapies approved in the United States.

FDA Table 1: Parkinson's disease therapies with associated adverse events

Drug Class	Agents	Common or Serious Adverse Events
Dopamine Agonists	Bromocriptine Pergolide Pramipexole Ropinirole	Somnolence/ sudden sleep attacks, dyskinesias, nausea, CNS effects (especially in elderly patients), cardiac valvulopathy (pergolide)
Catechol-O-methyl transferase (COMT) inhibitors	Entacapone Tolcapone	Hepatic toxicity (primarily with tolcapone, includes rare fatal cases), diarrhea
Anticholinergics	Artane Cogentin	Dry mouth, blurred vision, urine retention, other anticholinergic effects
Other	Amantadine	CNS effects

Table adapted from:

Hermanowicz N. Management of Parkinson's Disease. Postgrad Med 2001; 110(6):15-28.

Scott CC et al. Medical and surgical treatment of PD. Postgrad Med 1999; 106(2):41-52.

2.3 Proposed Rasagiline Labeling with Respect to Safety

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ ✓ § 552(b)(4) Draft Labeling

rasagiline as an adjunct to levodopa. Another listing categorized adverse events as occurring frequently (at least in 1/100 patients), infrequently (1/100 to 1/1000 patients) or rarely (less than 1/1000 patients) among all Parkinson's disease patients receiving rasagiline during phase II/III clinical trials.

Teva reports there were no significant differences in the safety profile based on age. No specific laboratory tests were recommended during rasagiline treatment.

Teva states that no cases of rasagiline overdose were reported in clinical development program, but that symptoms may resemble those observed with non-selective MAO inhibitors. Monitoring and general supportive treatment are advised.

2.4 Animal Pharmacology and Toxicology

Teva reports that the maximum non-lethal oral dose for rats and mice was approximately 100 mg/kg/day. The mechanism of death was thought to be functional neuropharmacological changes secondary to excessive doses of an inhibitor of the oxidation of biogenic amines.

Teva states that the principle manifestations of toxicity were related to loss of MAO selectivity, and included reduced food intake, weight gain and hyperactivity or aggression in rats. Teva reports that at higher oral doses these findings were sometimes associated with increases in liver weight and changes in hepatocyte morphology in rats. These changes were characterized as being consistent with those observed in rats treated with hepatic microsomal enzyme inducers. However, the sponsor notes that no studies measuring hepatic microsomal proteins were performed to support this hypothesis.

Teva assessed the effect of rasagiline on the cardiovascular system in three animal species: dogs, rats and cats. In the canine study, conscious animals acutely treated with rasagiline (3 mg/kg oral, the equivalent of ten-fold higher than the proposed human dose⁶) were monitored by telemetry. Teva states that rasagiline produced no overt treatment related changes in cardiovascular parameters during these canine studies. The sponsor also reports that rasagiline caused no effects on the cardiovascular system in cats (up to 1 mg/kg intravenous) or rats (when administered repeatedly at doses exceeding those required for selective MAO-B inhibition (Nonclinical Overview 2.4.2.3). No hERG channel assay studies were performed.

Reviewer comment: I was unable to locate statements within the Nonclinical Overview of animal studies addressing the effect of rasagiline on cardiac repolarization.

Teva reports that an Irwin screen in rats did not demonstrate potential for unwanted pharmacological actions on the central nervous system. The sponsor notes suspected changes in thyroid and bladder morphology occurring in a rat 13-week oral study, but states these were not corroborated by findings in either the 4-week or 26-week rat oral studies.

⁶ From Teva study TVA 147/003839, Pg. 8

Teva writes that rasagiline did not potentiate the hypertensive effect of levodopa/carbidopa when the drugs were repeatedly co-administered. The sponsor states there was no manifestation of the tyramine pressor response in rats at rasagiline doses of up to 0.5 mg/kg/day for 21 days.

During a 24-month carcinogenicity study in mice, higher than control incidences of combined bronchiolar/alveolar neoplasia (in both sexes) and of Harderian neoplasia (in males) were observed. Teva noted that very high dosages were used compared to proposed human administration, and that both these tumors occur frequently in the CD-1 mouse. Teva further noted that there was no evidence of carcinogenic effects in a rat 24-month study. Based upon these factors, as well as consideration of historical control data, statistical trend analysis and lack of pre-neoplastic lesions in chronic toxicity studies, Teva concluded that the observed increase in mouse lung and Harderian gland tumors did not constitute evidence of a carcinogenic hazard in humans.

Teva stated rasagiline showed no genotoxic potential during three independent *in vivo* studies. One of these studies was conducted in combination with levodopa/carbidopa.

Teva reports no impairment in fertility in rats given up to 3 mg/kg/day, more than 30 times the proposed human exposure. A potential to suppress lactation was seen at doses exceeding 3 mg/kg/day. An increased incidence of a rib malformation (“wavy rib”) was observed in rat fetuses from dams treated with rasagiline/levodopa/carbidopa, although the sponsor notes that this was a transient and reversible phenomenon. An increase in post-implantation loss was observed in rabbits treated with rasagiline at approximately six and one half times the recommended human dosage.

2.5 Human Pharmacokinetics

Teva states that rasagiline pharmacokinetics are linear for doses between 0.5 and 2 mg. Teva notes that while rasagiline has a terminal half-life of 0.6 to 2 hours, this is not associated with the length of its pharmacologic effect due to the irreversible inhibition of MAO-B. Rasagiline’s major metabolite, aminoindan, does not act as an MAO inhibitor.

Teva states that rasagiline reaches C_{max} in about 0.5 hours. Teva notes that because AUC (area under the curve) is not significantly affected by food (20% decrease), rasagiline may be administered with or without food (Clinical Overview 2.5.2.4.3). Plasma protein binding following a single oral dose of ^{14}C -labeled rasagiline was approximately 60-70% when measured 12 hours post-administration (Clinical Overview 2.5.3.4).

Teva indicates that CYP 1A2 is the major enzyme responsible for rasagiline metabolism. Teva states that co-administration of rasagiline and theophylline, a substrate of CYP 1A2, did not affect the pharmacokinetics of either drug. Co-administration of ciprofloxacin, a CYP 1A2 inhibitor, increased rasagiline AUC by 83% with no change in the elimination half-life (Clinical Overview 2.5.3.5). Teva writes that population pharmacokinetics analysis in patients treated with rasagiline as an adjunct to levodopa demonstrated that

oral clearance was not affected by co-administration of a variety of other drugs, including beta-blockers, ACE-inhibitors, COX-2 inhibitors and other Parkinson's disease therapies.

Teva notes that rasagiline differs from selegiline in that rasagiline is not metabolized *in vivo* to amphetamine or methamphetamine.

Teva reports that elimination of rasagiline is primarily via urine (62 %), and secondarily through feces (22%). Under 1% is excreted unchanged in the urine (Clinical Overview 2.5.3.6).

3. Approach to Safety Review/Methods

To evaluate the consistency of the safety data presented in the rasagiline NDA, including the 120-day safety update, I performed the following reviews:

1. Death narratives were crosschecked with the related data from the case report forms (CRFs), narrative summaries, electronic data sets and other sponsor tabulations.
2. For selected serious adverse events (SAEs) and adverse events (AEs) leading to study discontinuation, the CRFs, narrative summaries, data sets and study reports were reviewed.
3. In the Adverse Event coding dictionary (ISS Attachments 18.3), the investigator preferred term (PT) assigned to each verbatim AE term was assessed for suitability.
4. For selected events (including cases of melanoma, falls and sleep disorders), the coding was reviewed in more detail through examination of the CRFs, electronic data sets, narrative summaries, and/or study report listings to determine if the coded terms accurately reflected the described events.
5. Additional evaluations of the data included reviewing treatment-emergent AE risk calculations, lab and vital sign data analyses, and cardiac QT interval data. An analysis exploring the higher rates of AE reporting in the levodopa adjunct trial conducted within North America (PRESTO), in comparison to lower rates for the levodopa adjunct trial conducted outside North American (LARGO), is presented in Section 4.3 of this review.

4. Review Findings

4.1 Description of Data Source

4.1.1 Overview of Trials

Teva reports that 27 clinical studies were conducted during the rasagiline development program. These consisted of the following (ISS Attachments 18.1):

Eighteen Clinical Pharmacology Studies:

- Eight studies in healthy volunteers (including one each with co-administration of theophylline and ciprofloxacin); four studies in Parkinson's disease patients (with and without levodopa treatment); one study in patients with hepatic impairment; one study in patients with renal impairment; four studies with tyramine administration (in both healthy volunteers and as sub-studies in trials of Parkinson's disease patients).

Eight primarily Safety and Efficacy Studies:

- Three randomized placebo-controlled trials (TEMPO, LARGO and PRESTO) with their respective double blind active-control phases (TEMPO: TVP-1012/232 [active control], LARGO: TVP-1012/123, PRESTO: TVP-1012/135), followed by three open-label extensions (TEMPO: TVP-1012/233, LARGO: TVP-1012/124 and PRESTO: TVP-1012/135 OL).

One Special Population Study:

- One study in Alzheimer's disease patients.

In addition to the studies above, Teva initiated several cohort and other studies to examine issues regarding the relationship of melanoma and Parkinson's disease.⁷ A tabular listing of the studies in the rasagiline development program is provided in the attachments section of this review.

The initial NDA submission (dated September 5, 2003) summarized data on adverse events reported to Teva up through April 30, 2003; the database lock date for the 120-day safety update was September 11-29,⁸ 2003 (Section 1.1).

The sponsor states that the key safety data was collected from the three pivotal trials (Phase III studies TEMPO, PRESTO and LARGO) and from the Phase II study TVP-1012/231. These studies are summarized in Section 4.1.2 below. Teva reported that data from other phase II studies was not included in the ISS analysis due to the small number of participants receiving the indicated dose (exact number not specified). However, one of the analysis cohorts (Cohort 9 - all PD patients ever exposed to rasagiline) does contain data from Phase II subjects (ISS Section 1.1). Additional, uncontrolled safety data for participants receiving rasagiline in double-blind active treatment and open-label clinical studies was also pooled and presented within the ISS analysis cohorts. These sponsor-designated analysis cohorts are described in section 4.1.3 of this review.

4.1.2 Summary of Pivotal Trials

The three pivotal Phase III trials (one monotherapy and two as an adjunct to levodopa) and the Phase II study TVP-1012/231 are summarized below:

⁷ These are discussed in this review in Section 4.7: Special Safety Analysis: Melanoma within the Rasagiline Development Program

⁸ The exact lock date within September 2003 varied by study: Sept. 11 for TVP-1012/123 and 124 (LARGO Extension), Sept. 24 for TVP-1012/233 (TEMPO Extension) and Sept. 29 for TVP-1012/113

1. TEMPO (Rasagiline Monotherapy, Study TVP-1012/232) consisted of a multi-national (Canada and the United States) double-blind, six-month phase with three treatment groups (rasagiline 1 mg [134 subjects], 2 mg/day [132 subjects] and placebo [138 subjects]), followed by a six-month double-blind active treatment phase. Participants included 404 early Parkinson's disease patients (average PD duration of one year), the majority of whom had not been previously treated with an anti-Parkinson's disease medication. Subjects were prohibited from taking levodopa, dopamine agonists, selegiline or amantadine, but could receive anticholinergic medications if deemed necessary.

Patients completing the first 26 weeks or patients requiring whose symptoms required additional anti-PD therapy could start the second (active) phase of double-blind treatment in which all patients received rasagiline, 1 or 2 mg. Patients who received rasagiline in the first phase remained on their originally assigned dose, while placebo-treated participants were switched to rasagiline, 2 mg/day.

Three hundred eighty (380) patients entered the second phase. During this active treatment phase participants could begin an additional anti-PD therapy (dopamine agonists or levodopa) as per investigator discretion, and 32% (n=123) did so.

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

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

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

3. LARGO (Rasagiline Adjunct: Study TVP-1012/122) was a multi-center, multinational (Europe, Argentina and Israel), double-blind, parallel group trial conducted in 687 levodopa-treated Parkinson's disease patients who were experiencing motor fluctuations. Patients were randomly assigned to receive placebo (229 patients), rasagiline 1 mg/day (231 patients) or the COMT inhibitor entacapone (227 patients) for 18 weeks. This was followed by a nine-month double-blind active treatment phase, in

which subjects previously treated with placebo in the TVP-1012/122 study received rasagiline 1 mg/day, and patients previously treated with rasagiline or entacapone continued on their original treatment assignment. This resulted in approximately two thirds of the extension participants receiving rasagiline, and approximately one third receiving entacapone (TVP-1012/123 Study Report).

4. Phase II study TVP-1012/231 was a multi-center (United States), placebo-controlled, dose-ranging trial conducted in PD patients not treated with levodopa. The 56 participants were randomized to receive rasagiline 1 mg, rasagiline up to 2 mg, rasagiline up to 4 mg or placebo for a ten-week dosing period, followed by six weeks of post-drug evaluation.

4.1.3 Sponsor Analysis Cohorts

For analysis within the ISS, Teva divided participants in the rasagiline development program into the following nine cohorts (ISS 1.4 and 2.2).

Placebo-Controlled Cohorts:

Cohort 1: Placebo-Controlled Studies without Levodopa Treatment. This cohort consisted of 446 early PD patients treated with rasagiline 1 mg/day (N=149), rasagiline 2 mg/day (N=146), or placebo (N=151) without concomitant levodopa. Cohort members were subjects from the placebo-controlled phase of the monotherapy trial TEMPO and TVP-1012/231 (a ten-week, placebo-controlled study in 56 PD patients not previously treated with LD.)

Reviewer comment: *This cohort pools two studies of early PD patients not previously treated with LD, one lasting 26 weeks and the other 10 weeks. To evaluate the appropriateness of this combining safety data from these two studies, I assessed whether the AE risk profiles were similar. No formal test of heterogeneity was utilized, but by general comparison the two studies appeared to have similar AE profiles overall.*

The demographic characteristics of Cohort 1 members are summarized in the table below.

FDA Table 4: Demographic Characteristics of Cohort 1 (Sponsor ISS Table 19)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		Rasagiline 1 mg (N=149)	Rasagiline 2 mg (N=146)	Placebo (N=151)	All (N=446)
Sex					
Female	n (%)	49 (32.9)	62 (42.5)	48 (31.8)	159 (35.7)
Male	n (%)	100 (67.1)	84 (57.5)	103 (68.2)	287 (64.3)
Age (Years)		Mean (Std)	61.8 (10.1)	60.9 (11.0)	61.3 (10.6)
<65	n (%)	85 (57.0)	82 (56.2)	86 (57.0)	253 (56.7)
>=65	n (%)	64 (42.9)	64 (43.8)	65 (43.0)	193 (43.2)
Race					
Caucasian	n (%)	141 (94.6)	143 (97.0)	142 (94.0)	425 (95.3)
Black	n (%)	3 (2.0)	2 (1.4)	2 (1.3)	7 (1.6)
Hispanic	n (%)	2 (1.3)	1 (0.7)	2 (1.3)	5 (1.1)
Asian	n (%)	3 (2.0)	-	4 (2.6)	7 (1.6)
American Indian	n (%)	-	1 (0.7)	-	1 (0.2)
Weight (kg)	Mean (Std)	77.6 (14.6)	80.7 (14.7)	78.0 (15.9)	78.7 (15.1)
Height (cm)	Mean (Std)	171.4 (9.0)	171.8 (9.6)	171.7 (9.7)	171.6 (9.4)
Body Mass Index (BMI, kg/m ²)	Mean (Std)	26.3 (3.9)	27.4 (4.4)	26.4 (4.5)	26.7 (4.3)
Disease Duration (Years)	Mean (Std)	1.0 (1.4)	1.1 (1.3)	0.9 (1.1)	1.0 (1.3)
Hoehn & Yahr Stage	Mean (Std)	1.8 (0.5)	1.8 (0.5)	1.8 (0.5)	1.8 (0.5)
Total UPDRS Score	Mean (Std)	24.7 (11.3)	25.9 (9.5)	24.5 (11.6)	25.0 (10.8)

Cohort 2: Placebo-Controlled Studies in Levodopa-Treated Fluctuating Patients.

This cohort combined data collected from the rasagiline 1 mg/day (N=380) and placebo (N=388) groups from the LARGO and PRESTO trials of rasagiline as adjunct to levodopa. Approximately 64% of subjects were receiving concomitant dopamine agonists (ISS Table 56.)

Reviewer comment: Data for rasagiline (0.5 mg) and entacapone were not summarized in the ISS, but was provided in the clinical study reports for PRESTO and LARGO, respectively.

The demographic characteristics of Cohort 2 members are summarized in the table below.

FDA Table 5: Demographic Characteristics of Cohort 2 (Sponsor ISS Table 20)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)	Placebo (N=388)	All (N=768)
Sex				
Female	n (%)	127 (33.4)	152 (39.2)	279 (36.3)
Male	n (%)	253 (66.6)	236 (60.8)	489 (63.7)
Age (Years)				
	Mean (Std)	63.6 (9.0)	64.8 (9.2)	64.2 (9.1)
<65	n (%)	203 (53.4)	186 (47.9)	389 (50.6)
>=65	n (%)	177 (46.6)	202 (52.0)	379 (49.4)
Race				
Caucasian	n (%)	363 (95.5)	371 (95.6)	734 (95.6)
Black	n (%)	3 (0.8)	1 (0.3)	4 (0.5)
Hispanic	n (%)	12 (3.2)	12 (3.1)	24 (3.1)
Other	n (%)	2 (0.5)	1 (0.3)	3 (0.4)
American Indian	n (%)	1 (0.3)	-	1 (0.3)
Weight (kg)	Mean (Std)	75.2 (15.0)	74 (14.8)	74.6 (14.9)
Height (cm)	Mean (Std)	169.8 (9.7)	168.1 (10.4)	168.9 (10.1)
Body Mass Index (BMI, kg/m ²)	Mean (Std)	26.0 (4.2)	26.1 (4.4)	26.0 (4.3)
Disease Duration (Years)	Mean (Std)	8.7 (5.1)	9.2 (4.8)	9.0 (5.0)
Hoehn and Yahr Stage "ON"	Mean (Std)	2.1 (0.6)	2.1 (0.7)	2.1 (0.6)
Hoehn and Yahr Stage "OFF"	Mean (Std)	2.7 (0.7)	2.8 (0.7)	2.8 (0.7)
Total UPDRS Score "ON"	Mean (Std)	31.5 (16.9)	31.6 (17.3)	31.6 (17.1)
Levodopa Treatment Duration (Years)	Mean (Std)	7.6 (4.9)	8.0 (4.7)	7.8 (4.8)
Total Levodopa Daily Dose (mg)	Mean (Std)	757 (395)	746 (388)	752 (341)
Fluctuation Duration (Years)	Mean (Std)	3.5 (3.2)	3.7 (3.1)	3.6 (3.1)
Total daily "OFF" Time (hours)	Mean (Std)	5.9 (2.5)	5.7 (2.4)	5.8 (2.4)
Dyskinesia* Duration (Years)	Mean (Std)	3.8 (3.6)	4.0 (3.0)	3.9 (3.3)
Use of Dopamine Agonists	n (%)	247 (65)	241 (62.1)	488 (63.5)
Use of Entacapone (only in PRESTO)	n (%)	49 (12.9)	61 (15.7)	110 (14.3)

*A total of 465 patients experienced dyskinesias: 221, and 244 in the rasagiline 1 mg and placebo, respectively.

Rasagiline-Treatment Cohorts:

Cohort 3: Rasagiline Monotherapy – Any Treatment Duration. Teva described this cohort as including 377 patients treated with rasagiline monotherapy from TEMPO (both phases) and its open-label extension (TVP-1012/233). Patients could not be taking dopamine agonists at the time of entry into TEMPO; however, approximately 46% of the cohort had dopamine agonists added to their PD regimen during the trial and its extension (ISS 8.1.2.1).

Reviewer comment: Unlike the monotherapy Cohort 1, which pooled the placebo-controlled portion of TEMPO with the much smaller study TVP-1012/231, in Cohorts 3 and 4 only data from the Phase III trial TEMPO and its extension was utilized.

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

Cohort 5: Rasagiline Treatment: Rasagiline Treatment in LD-Treated Non-Fluctuating Patients – Any Treatment Duration. This cohort was composed of 154 participants from TEMPO (the active treatment phase), and/or its open label extension for

which levodopa therapy was added to rasagiline monotherapy. The sponsor states that some of the patients in this cohort may have become fluctuators as their disease progressed.

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

Cohort 7: Active Treatment: LD-Treated Fluctuating Patients – Any Treatment Duration. This cohort consists of fluctuating PD patients treated with rasagiline adjunct therapy in studies LARGO, the LARGO extension (TVP-1012/123), PRESTO, the PRESTO extension (TVP-1012/135), TVP-1012/112⁹ and its extension (TVP-1012/113).

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

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

Reviewer comment: Cohort 9 does contain data on some participants from clinical pharmacology studies, but only those with Parkinson's disease. Information on healthy volunteers and other subjects without PD are not contained in this cohort.¹⁰

Cohorts Most Frequently Utilized

The cohorts most frequently utilized in this safety review were Cohort 1 (which encompassed placebo-controlled rasagiline monotherapy participants, mostly drawn from the TEMPO trial), Cohort 2 (for placebo-controlled studies of rasagiline as an adjunct to levodopa, drawn from LARGO and PRESTO), and Cohort 9 (all subjects with PD ever exposed to rasagiline).

4.2 Summary of Exposure

4.2.1 Number of Subjects

A total of 1935 subjects participated in the rasagiline clinical development program, including 1360 patients with Parkinson's disease (120 Day Safety Update 2.1.1). The following table summarizes the number of subjects exposed to rasagiline, placebo and entacapone by study:

FDA Table 6: Number of Participants Exposed to Rasagiline and Placebo by Study (Adapted from Sponsor Table 1, 120 Day Safety Update):

⁹ TVP-1012/112 is a double-blind, randomized, placebo-controlled trial in LD-treated PD patients receiving 0.5 mg rasagiline, 1.0 mg rasagiline or placebo for 12 weeks.

¹⁰ Communication from Teva representative, 3/6/2004

Protocol Number	Number of Subjects		
	Rasagiline - Any Dose	Placebo	Entacapone
TEMPO*+TVP-1012/233**	398	138	--
PRESTO+TVP-1012/135	436	159	--
LARGO+TVP-1012/123 + TVP-1012/124	395	229	227
TVP-1012/112+TVP-1012/113	63	13	--
TVP-1012/132	14	6	--
TVP-1012/121	4	1	--
TVP-1012/231	43	13	--
TVP-1012/111	7	3	--
Others***	177	34	--
All	1537	596	227

*Includes both the placebo-controlled and the double-blind, active-control portions of TEMPO

**TVP-1012/113 and 233 up to September 3, 2002 cut-off date. (Section 1.3)

*** Includes Phase I and Alzheimer Disease Patient Studies

Exposure by Cohort

The rasagiline exposure accumulated in the various ISS analysis cohorts are provided below. *Reviewer comment:* Placebo exposures for the two placebo-controlled cohorts were: Cohort 2: 147.3 person years (388 participants).

FDA Table 7: Rasagiline Exposure by ISS Cohorts* (Adapted from ISS 2.1 and 120 Day Safety Update 2.1.2.2)

Cohort	# of Rasagiline Participants	Patient-Years (PYs)
1: Placebo-Controlled Monotherapy	295	64.2 (1 mg) 62.6 (2 mg) 65.8 (Placebo)
2: Placebo-Controlled Levodopa Adjunct	380	146.7 (1 mg) 147.3 (Placebo)
3: Rasagiline Monotherapy – Any Duration	377	585.6
4: Rasagiline Monotherapy – Long Term	252	797.0
5: Levodopa, Non-Fluctuating Patients – Any Duration	183	335.2
6: Levodopa, Non-Fluctuating Patients – Long Term	108	304.3
7: Levodopa, Fluctuating Patients – Any Duration	666	582.7
8: Levodopa, Fluctuating Patients – Long Term	249	349.6
9: All PD Patients Ever Exposed to Rasagiline	1360	2017.3

*Note: As the cohorts are not mutually exclusive, the sum of the patient-years for cohorts 1-8 exceeds that of Cohort 9.

Postmarketing Exposure

As rasagiline has not been previously marketed, no post-marketing data is available.

4.2.2 Exposure by Duration

Teva summarized cumulative participant exposure by duration in the table below.

FDA Table 8: All Subjects Ever exposed to rasagiline: distribution of subjects by cumulative treatment duration (Adapted from Sponsor ISS Table 5)

All Subjects Ever Exposed to Rasagiline	Rasagiline	
	N	%
Ever Exposed ¹¹	1360	100.00
≥ 3 months	1197	88.01
≥ 6 months	1028	75.59
≥ 12 months	674	49.56
≥ 2 years	282	20.74
≥ 3 years	245	18.01

4.2.3 Exposure by Dose and Duration

Teva states that subjects in Cohort 1 (placebo-controlled rasagiline monotherapy) accumulated 64.2 PYs of exposure (149 patients) to 1 mg/day and 62.6 PYs of exposure (146 patients) to 2 mg/day. The median time of exposure for each treatment group was about 182 (range 5-204) days (ISS 2.2.1.1). Just over half (51.7 %) of subjects were exposed to the proposed rasagiline dose (1 mg/day) for between 18 and 26 weeks, while an additional 28.2 % were exposed for between 26 and 30 weeks (ISS Table 11).

Reviewer comment: *The placebo-controlled phase of TEMPO lasted 26 weeks, so subjects with 26 or more weeks of exposure were presumably those completing the placebo-controlled portion. However, the TEMPO study report (page 8) states that 382 subjects of the 404 randomized completed the placebo-controlled phase, while the total subjects in the 18 Week to 26 Week, and 26 Week to 30 Week categories of ISS Table 11 was 350. It is therefore unclear whether subjects with 26 weeks of exposure were equivalent to those completing the placebo-controlled portion of TEMPO.*

In Cohort 2 (placebo-controlled levodopa adjunct therapy), approximately 146.7 PYs of exposure to rasagiline 1 mg/day was accumulated by the 380 subjects included in the cohort. The median time of exposure was 129 (range 3-212) days (ISS 2.2.1.2). Most participants (54.4 %) were exposed to rasagiline (1 mg/day) for between 18 and 26

¹¹ The “ever exposed” number in FDA Table 6 (N=1360) does not match FDA Table 4 “All” (N=1537) because Table 6 does not include the additional information from the safety update.

weeks, while an additional 16.6 % were exposed between 26 and 30 weeks (ISS Table 12).

Teva did not provide an integrated tabular summary of exposure by both dose and duration within the ISS or the 120 Day Safety Update. However, with respect to ICH guidelines, 1028 patients were exposed to rasagiline at any dosage for at least six months, and 674 patients were exposed for at least 1 year. As calculated from subjects receiving the indicated 1 mg/day dose in the three pivotal trials (TEMPO, PRESTO and LARGO), ICH guidelines were met for subjects exposed to the proposed dose for both six months and one year (ISS 2.2.1.2). In addition, Teva reports that 1537 subjects were exposed to rasagiline at any dose, exceeding the ICH recommendation of 1500 subjects (120 Day Safety Update 2.1.1).

Teva summarized the exposures of all PD patients (Cohort 9) by dose of rasagiline in the following table:

FDA Table 9: Distribution of Cohort 9 (All PD Patients Exposed to Rasagiline) by Rasagiline Dose (Sponsor 120 Day Safety Update Table 4)

		Rasagiline Dose													
0.5 mg		0.5 or 1* mg		1 mg		1 or 2** mg		2 mg		4 mg		10 mg		All	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
136	10.0	96	7.1	703	51.7	296	21.8	110	8.1	14	1.0	5	0.4	1360	100.0

*Patients who were treated with rasagiline 0.5 mg in the double-blind study TVP-1012/135 continued on 1 mg in its open-label extension

**Patients who initially were treated with rasagiline 2 mg in the double-blind TEMPO study and/or in its open-label extension TVP-1012/233 continued treatment on 1 mg

Duration of exposure to the proposed dose (1 mg/day) for placebo-controlled rasagiline monotherapy (Cohort 1), and rasagiline therapy as an adjunct to levodopa (Cohort 2) are provided in the section 4.2.2.

4.2.4 Exposure by Age

Teva reports that the mean age for all participants in the placebo-controlled rasagiline monotherapy studies (Cohort 1) was 61.3 years (range 33 to 92). Mean ages were 61.8 years (Median 63.1) for rasagiline 1 mg/day, 60.9 years (Median 63.0) for rasagiline 2 mg/day, and 61.3 years (Median 62.1) for placebo (ISS Section 3.1.1).

For rasagiline as an adjunct to levodopa therapy (Cohort 2), the mean age for all participants was 64.2 years (range 33 to 87) for total participants, 63.6 years for rasagiline 1 mg/day, and 64.8 years for those receiving placebo (ISS Section 3.1.2).

For all PD patients exposed to rasagiline (Cohort 9), age data was not presented as a mean; however, 676 patients (57%) were below 65 years of age and 511 participants (43%) were older than 65 years (ISS 2.1.2.2.2).

4.2.5 Exposure by Sex

For the 1360 Parkinson's disease patients exposed to rasagiline (Cohort 9), there was an overall male predominance (64.4%) (ISS 2.1.2.2.2). A roughly equivalent percentage of early Parkinson's disease patients treated with rasagiline without levodopa (Cohort 1) were female (32.9%), compared to those treated with placebo (31.8%). Thirty three percent of rasagiline-treated (1 mg/day) levodopa adjunctive participants (Cohort 2) were female, versus 39.2 % in the placebo group (ISS 3.1.2).

4.3 Review of AE Surveillance and Coding of AEs

Teva states that adverse events (AEs) were elicited during all study visits through open-ended questioning (ISS 6). The sponsor reported that events were recorded in the Adverse Event log regardless of whether they were considered drug-related. Teva states that special attention was paid to the following categories: cardiovascular events, malignancies, and symptoms potentially associated with MAO inhibition¹² or hypertensive reactions.¹³ In Cohort 2, AEs were further classified by concomitant medication use.¹⁴ Parkinson's disease symptoms were considered AEs "only if they had worsened beyond what would be expected in the normal progression of the disease (ISS 6)."

Reviewer comment: This practice regarding PD symptoms could potentially fail to register some events, such as orthostatic hypotension, which may be attributed to either PD or the study drug. However, in blinded trials one would expect any misclassification or underreporting to be non-differential between the placebo and treatment groups.

Teva reports that investigator verbatim terms describing AEs were standardized to preferred terms via the Coding Symbols for Thesaurus of Adverse Reaction Types (COSTART) (ISS 5.1). The sponsor states a "worst case scenario" was utilized, with events such as orthostatic or postural dizziness coded as postural hypotension (ISS 1.5.5). The sponsor asserted that differing terminology for AEs and study drug action in the various studies was translated to uniform terms for analysis (ISS Post-Text Table 1.)

The sponsor calculated "incidence" of AEs as the percent of subjects reporting (at least once) a specific AE out of the total number of patients in that group. The sponsor term "frequency" was defined as the number of distinct reports of (not subjects affected by) the same AE. For the placebo-controlled cohorts, as exposure was comparable for treatment groups, risk (percent) was used for determining AE relative frequency instead

¹² The sponsor included the following symptoms as being potentially associated with MAO inhibition: nausea, hallucinations, confusion, depression, loss of balance, insomnia and orthostatic hypotension

¹³ The sponsor included severe headache as a potential symptom of hypertensive crisis.

¹⁴ AEs reported by Cohort 2 participants were further classified by use of selected drugs: dopamine agonists, amantadine, entacapone, antidepressants, SSRI, antimuscarinic [anti-Parkinsonian] agents, and drugs of the anxiolytic/sedative/hypnotic/neuroleptic group.

of rate (ISS 1.5.5.1).¹⁵ In the rasagiline-treatment cohorts Teva utilized the number of reports standardized to exposure in terms of 100 patient years (PYs), as it was considered to be the more appropriate method for presenting relative occurrence (ISS 1.5.5.1).

Reviewer comment: *The sponsor typically presented AE rates as the number of events per total PYs of exposure, as opposed to the number of patients affected per total PYs of exposure. This creates some difficulties in interpretation: the rate for one subject experiencing ten events would be the same as for ten subjects experiencing one event each. For events of particular interest, I re-calculated the rate as the number of subjects affected per 100 PYs.*

The sponsor defined a serious adverse events (SAE) as an AE resulting in any of the following: death, a life threatening condition, hospitalization or prolongation of an existing hospitalization, a persistent or significant disability, a congenital anomaly, or an important medical event that may have required medical or surgical intervention to prevent any of the above (PRESTO study report 7.6.2.1). Significant AEs were defined as those resulting in action being taken with the study drug, such as a dose change, interruption or discontinuation (ISS 6.8.1). AEs were further classified as mild (easily tolerated), moderate (sufficiently discomforting to interfere with daily activity) and severe (preventing normal every day activities.) (TEMPO study report, 9.5.2.1).

In the placebo-controlled cohorts, common AEs were defined as AEs occurring in at least 2% of patients in the rasagiline 1 mg group, and more frequently than in the placebo group (ISS 5.3). In the rasagiline-treated cohorts, common AEs were defined as AEs with at least ten reports per 100 patient years (PYs).

Reviewer comment: *To evaluate the appropriateness of the designation of ten reports per 100 PYs in the uncontrolled cohorts as “common” AEs, I compared whether AEs that met criteria for common by the criteria for the placebo-controlled cohorts (reported by least 2% of rasagiline-treated subjects, and more frequent than in the placebo group) were also “common” in Cohort 9 (all PD patients exposed to rasagiline) by the criteria of ten reports per 100 PYs. The table below summarizes the correspondence between designation of AEs as common by the criteria of the placebo-controlled cohorts and the uncontrolled cohorts for a sample of common AEs in the placebo-controlled cohorts.*

FDA Table 10: Comparison of Designation of AEs as Common by Criteria for Controlled and Uncontrolled Cohorts

Adverse Event	Common by Controlled Cohorts Criteria	Common by Uncontrolled Cohort
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¹⁵ As an illustration of the equivalent exposures between treatment arms in the placebo-controlled trials, the exposure data for the three treatment groups in PRESTO were: (1) *Rasagiline 0.5 mg*: 164 subjects, 76.2 patient-years, median treatment 183 days (2) *Rasagiline 1.0 mg*: 149 subjects, 69.6 patient-years, median treatment 183 days (3) *Placebo*: 159 subjects, 73.8 patient-years, median treatment 183 days (PRESTO Study Report 10.1).

		Criteria*
Headache	Yes (14% Cohort 1)	Yes (15 repts./100PYs)
Dizziness	Yes (11% Cohort 1)	Yes (13 repts./100 PYs)
Dyskinesia	Yes (10% Cohort 2)	Yes (10 repts./100 PYs)
Arthralgia	Yes (7.4% Cohort 1)	Yes (11 repts./100 PYs)
Flu Syndrome	Yes (6% Cohort 1)	No (4.8 repts./100 PYs)
Weight Loss	Yes (4% Cohort 2)	No (3.1 repts./100 PYs)

* AE rates and percents were taken from the 120 Day Safety Update Post-Text Table 84 [Cohort 9], ISS Post-Text Table 68 [Cohort 1], and ISS Post-Text Table 69 [Cohort 2]

While there were two discrepancies in the designation of AEs as common by the two methods (for flu syndrome and weight loss), one would expect some variation in the occurrence of AEs between the cohorts, and both were among the less frequently reported (by percentage) of the common AEs. The use of ten reports per 100 PYs is therefore an acceptable criterion for identifying common AEs in the uncontrolled cohorts. However, as noted above, for AEs of particular interest I also calculate the rate as the number of subjects affected per 100 PYs. It is also noted that the criteria for the placebo-controlled cohorts (least 2% of patients in the rasagiline 1 mg group, and more frequently than in the placebo group) appears to be more inclusive.

The sponsor notes that AE reporting differed between the two Phase III levodopa adjunct studies; with 90% of the PRESTO (North America) participants and 50% of LARGO (Europe, Argentina and Israel) participants reporting AEs. Teva hypothesized that this difference may be due to the longer duration of PRESTO (26 weeks versus 18 weeks in LARGO) or to cultural variations among study sites. Despite the differences in AE reporting between the two trials in both the rasagiline and placebo arms (see tables below), for the Cohort 2 analysis in the ISS (ISS 6), Teva pooled the rasagiline (1 mg) and placebo groups from each study, as both studies were placebo-controlled.

***Reviewer comment:** Given the large difference in AE reporting between the two levodopa adjunct studies (PRESTO and LARGO) combined within Cohort 2, I examined the issue further, including comparing the difference in AEs for the various treatment groups. Table 9 below presents the percentage of subjects who experienced AEs and the mean number of AEs per subject, and demonstrates that both were elevated in PRESTO compared to LARGO.*

FDA Table 11: Percent of Subjects with AEs and Mean Number of AEs Per Subject by Treatment Group in Studies PRESTO and LARGO

	PRESTO		LARGO		
	Rasagiline (1 mg)	Placebo	Rasagiline (1 mg)	Entacapone	Placebo
% of Subjects with AEs	95	87	47	56	47
Mean # of AE per	4.5	4.0	1.2	1.2	1.0

Subject					
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Adverse events figures calculated from PRESTO 10.2.5 and LARGO 12.2.1.1 Table 40.

Table 10 below compares the frequency of a sample of common, potentially drug-related AE preferred terms for the two trials. The frequency of specific AE terms was considerably higher in both the rasagiline and placebo treatment arms in the US-based study (PRESTO), compared to the non-US LARGO.

FDA Table 12: Frequency of Specific AE Preferred Terms in PRESTO and LARGO

	PRESTO		LARGO	
	Rasagiline	Placebo	Rasagiline	Placebo
Dyskinesia	18.1%, n=27	10.1%, n=16	5.2%, n=12	3.9%, n=9
Nausea	12.1%, n=18	8.2%, n=13	3.5%, n=8	4.4%, n=10
Dizziness	9.4%, n=14	9.4%, n=15	2.6%, n=6	1.7%, n=4
Hypotension postural	8.7%, n=13	3.1%, n=5	2.2%, n=5	0

Table 11 below compares the reporting of total adverse events with the reporting of serious adverse events (SAEs) for the two trials.

FDA Table 13: Percent of Subjects Experiencing AEs and SAEs by Treatment Group in the Studies PRESTO and LARGO

	PRESTO		LARGO		
	Rasagiline (1 mg)	Placebo	Rasagiline (1 mg)	Entacapone	Placebo
% of Subjects with AEs	95	87	47	56	47
% of Subjects with SAEs	12	9	5.2	5.3	7.4

Information taken from LARGO (Pg. 7, Pg. 141) and PRESTO (Pg 137, Pg. 143) study reports

The percent of rasagiline-treated subjects experiencing both AEs and SAEs in the PRESTO trial were roughly twice as high as in LARGO. The percent of placebo subjects reporting AEs were also considerably higher in PRESTO, although less so for SAEs than AEs.

The development program for another Parkinson's disease therapy¹⁶ also demonstrated a trend of lower AE rates in studies conducted at sites outside of North America, compared to those using North American participants. However, in this previous review of differential rates of AE reporting based on geographic location, the analysis revealed

¹⁶ FDA Safety Review (dated September 30, 1999) prepared by Dr. Judy Racoosin

that the increased AE reporting in North American studies was observed primarily for total AEs, and considerably less so for SAEs. This trend could be explained by cultural variations affecting the reporting of less concerning or more subjective AEs, but not of the more serious AEs. That this pattern is not seen when the rasagiline-treated subjects in LARGO and PRESTO were compared is more difficult to explain. However, given this significant difference in AE reporting between the two adjunctive studies combined to form Cohort 2, in this review I will also present and analyze AE data individually for PRESTO and LARGO as well as for Cohort 2 as a whole.

4.4 Audit Findings and Evaluation of the AE Coding

In auditing the rasagiline safety database, I compared data for laboratory studies and vital signs for selected rasagiline participants (among those with serious AEs or AEs leading to discontinuation) across available data sources, including CRFs, ISS text and post-text tables. I found concurrence between the various sources.

I reviewed the coding of investigator verbatim terms to preferred terms within the AE coding dictionary (ISS Attachments 18.5). With the exceptions discussed below, there was general agreement between investigator and verbatim terms.

Within the AE dictionary, I identified several instances of splitting a given verbatim term between different preferred terms. The most notable example of this pertained to the coding of falls. In the NDA dataset AE9, which contained adverse events for all Parkinson's disease patients ever exposed to rasagiline, 192 verbatim descriptions related to the occurrence of a fall.¹⁷ The majority (160) of these were coded to the COSTART term accidental injury. The remaining 32 were coded to the following categories: overdose (1), cerebrovascular accident (1), syncope (3), arthralgia (1), myalgia (1), abnormal gait (1), ataxia (8), confusion (1), dizziness (4), dyskinesia (2), extrapyramidal syndrome (6), and urinary symptoms (3).

A number of verbatim descriptions were noted to contain more than one adverse event, typically paired in a precipitant-and-effect manner. Examples of this included: "Vomiting due to upset stomach" (coded to dyspepsia), or "feels tired, lower back ache" (coded to back pain). This occurred frequently for falls, with falls being treated as both a precipitant ("left leg pain secondary to fall" [coded to accidental injury]) and an effect ("fall secondary to left hamstring tightness" [coded to myalgia].)

This reviewer requested that the sponsor address this disparate coding of falls by creating a new preferred term (PT) "FALLS" to be placed in the Body as a Whole organ system category. Fall-related verbatim terms that named two or more events were to be coded to both the FALLS PT and a reasonable PT for the precipitant or resultant verbatim term. In addition, this reviewer requested that cold/upper respiratory (URI) infections be removed from "INFECTIONS" to a new PT "COLD," and that several cases of "stomach-flu" be re-classified under the PT "GASTROENTERITIS." These coding changes were

¹⁷ Verbatim descriptions which contained the keywords fall, falls, falling or fell, or which otherwise pertained to falls upon review.

submitted within the 120 Day Safety Update, Section 7.3. I reviewed the re-coded verbatim terms provided in Attachments 10.2.2.2 of the 120 Day Safety Update, and found the coding to be appropriate.

More minor examples of splitting were observed. For example, helicobacter pylori infection, knee replacement surgery, muscular stiffness, regurgitation, hematuria, radiculopathy and knee swelling were occasionally coded to different but generally acceptable preferred terms. These lesser examples would not be expected to impact the overall safety analysis. Rare instances of possibly inappropriate coding were identified (for example, “mind racing + over talkative” coded as abnormal thinking, when it likely would have been more precisely coded as manic reaction.)

4.5 Clinical Pharmacology Studies: Safety

At the request of this reviewer, Teva summarized data from the Clinical Pharmacology Studies within the rasagiline development program in an NDA supplement, the Phase I/II Safety Update, submitted March 2004. The sponsor presented data for a total of 187 healthy volunteers, 17 subjects with hepatic impairment and 16 subjects with renal impairment who were participants in fifteen Phase I/Clinical Pharmacology studies (Phase I/II Safety Update 2.1).

Reviewer comment: *Phase II study TVP-1012/231 was combined with the placebo-controlled portion of the Phase III study TEMPO to form ISS analysis Cohort 1. Study TVP-1012/231 was not among the phase II studies addressed in the Phase I/II Safety Update (Phase I/II Safety Update Section 2.1.1.2), so there was no overlap of subject data between the safety update and ISS Cohort 1. As ISS Cohort 9 included all PD subjects exposed to rasagiline, there is some overlap of subject data between Cohort 9 and the Phase I/II Safety Update.*

In their analysis, Teva presented data for the following four groups:

1. *Phase I Studies in Healthy Volunteers:* This cohort contained 156 healthy subjects participating in nine studies.
2. *Placebo-Controlled Phase II Studies in Levodopa-Treated PD Patients:* This cohort consisted of 105 levodopa-treated patients, (82 rasagiline, 23 placebo) who participated in four placebo-controlled Phase II/Clinical pharmacology studies, including one pharmacodynamic study with tyramine.
3. *Special Population - Hepatic Compromise:* This cohort contained subjects with hepatic impairment (n=17) and matched (on age, weight and sex), healthy control subjects.
4. *Special Population - Renal Compromise:* This cohort contained subjects with renal impairment (n=16) and matched (on age, weight and sex), healthy control subjects.

Matched, control subjects from the studies of subjects with hepatic impairment (TVP-1012/424) and renal impairment (TVP-1012/425) were included among the 156 subjects within the Healthy Volunteer cohort (Phase I/II Safety Update 2.1.1.1).

The tables below summarize the details of the trials in the three subject populations (healthy volunteers, Parkinson's disease patients and patients with renal or hepatic impairment).

FDA Table 14: Phase I Study Designs on for Healthy Subjects and Subjects with Renal or Hepatic Impairment (Sponsor Phase I/II Safety Update Table 1)

Study No.	Double-Blind	Open-Label	Parallel	Crossover	Single Dose	Multiple Dose	Placebo-Controlled	Ascending Dose	Concomitant Disease	Drug/Pharmacodyn. Interaction
CC547	X			X (4 periods)	X		X	X		
CD596	X		X			X	X			
TVP-1012/422		X			X					
TVP-1012/421		X		X	X					
TVP-1012/423		X		X	X					
TVP-1012/427		X		X	X					
TVP-1012/424		X	X			X			Hepatic	
TVP-1012/425		X	X			X			Renal	
TVP-1012/426		X				X				Ciprofloxacin
TVP-1012/430	X		X			X	X			Theophylline
P94159	X		X			X	X			Tyramine

FDA Table 15: Phase I Study Designs for Subjects with Parkinson's disease (Sponsor Phase I/II Safety Update Table 2)

Study No.	Double-Blind	Placebo-Controlled	Parallel	Ascending Dose	Sequential	Pharmacodynamic Interaction
TVP-1012/111	X	X	X	X		
TVP-1012/112	X	X	X			
TVP-1012/121	X	X	X	X		
TVP-1012/132	X	X			X	Tyramine

4.5.1 Clinical Pharmacology: Exposure

Teva reports that the 187 healthy subjects fell into the following treatment groups: 122 received rasagiline, 31 received placebo and 34 received placebo/rasagiline during crossover studies. The sponsor states that approximately one third of the 187 subjects participated in drug interaction studies in which they were also administered theophylline (TVP-1012/430) or ciprofloxacin (TVP-1012/426), or were challenged with high doses of tyramine (P94159) (Phase I/II Safety Update, Pg. 3).

Teva states that the 156 participants in the Healthy Volunteers Cohort were exposed to approximately 2.9 PYs of rasagiline administration over a period of 11.1 total years.¹⁸

¹⁸ Total years were defined as the time from the first dose until "last observed value." The criteria for last observed value was not clearly defined within the Phase I/II Safety Update, but from the protocols of the

Median days of exposure for this cohort were not provided by the sponsor (Phase I/II Safety Update 3.1), although in the sponsor table above five of the nine studies in healthy volunteers were single dose studies.

The sponsor noted that the vast majority of subjects were exposed to rasagiline at doses higher than the proposed 1 mg/day, with some as high as 10 mg/day. The control group (which consisted of “naïve” subjects who were not exposed to rasagiline throughout the study, or subjects who switched from placebo to rasagiline) accumulated four total PYs (Phase I/II Safety Update, Pg. 3).

The maximum dose of rasagiline that human subjects were exposed to was 20 mg/day (Study CC547). Teva reports that four of the fourteen rasagiline-treated subjects in CC547 experienced adverse events, which included the following (CC547 Table 15):

- Rasagiline 1 mg: dryness in mouth/thirst, bacterial respiratory infection
- Rasagiline 2 mg: headache
- Rasagiline 5 mg: asthenia
- Rasagiline 10 mg: abdominal pain

Subjects receiving placebo also reported nausea, headache, abdominal pain and asthenia.

Teva states that the vast majority of participants in the levodopa-treated PD Patient cohort also received doses higher than 1 mg/day. The sponsor reports that approximately 16.6 PYs of exposure to rasagiline had been accumulated by the 82 rasagiline-treated members of this cohort (Phase 1 Safety Update, Pg. 3). Median exposure times and cumulative dosages are given in the table below:

FDA Table 16: Levodopa-Treated PD Patients: Median Total Exposure (Sponsor Table 4, Phase 1 Safety Update)

Rasagiline ISS: Placebo-Controlled Phase II/Clinical Pharmacology Studies: Levodopa-Treated PD Patients	Rasagiline 0.5 mg (N=21)	Rasagiline 1 mg (N=28)	Rasagiline 2 mg (N=28)	Rasagiline >2 mg (N=5)	Placebo (N=23)
Median Total Exposure (Days)	85.0	82.5	85.0	37.0	83.0
Median Total Dose (mg)	42.0	82.5	170.0	171.0	0.0

The sponsor did not present person-years of exposure for the hepatic and renal impairment cohorts.

4.5.2 Clinical Pharmacology: Mortality

Teva states no deaths occurred among subjects participating in the Phase I/II studies.

4.5.3 Clinical Pharmacology: Serious Adverse Events

individual studies the last observed value generally appears to be the time of last vital sign measurement or phlebotomy for laboratory testing.

Phase I/Healthy Volunteers: Teva reported no SAEs in this cohort among rasagiline-treated subjects (Phase 1 Safety Update 7.1.5.1). One SAE (paranoid reaction) was reported in a healthy volunteer on placebo who subsequently discontinued the study,

Phase II/LD-treated PD patients: The sponsor states that SAEs were reported for one placebo participant (deterioration of PD) and two rasagiline-treated participants (summarized below) within this cohort:

TVP-1012/111 #803: On study drug day 28 (one day after the subject's rasagiline dose was reduced from 10 mg to 5 mg), this 64 year-old woman experienced "orthostatic syncope" which resulted in hospitalization and withdrawal from the study. She had previously experienced AEs of hypertension, myalgia and headache.

TVP-1012/111 #808: While receiving rasagiline 10 mg, this 58 year-old woman experienced hypertension (220/120) on study drug day 28 which resulted in hospitalization and study discontinuation. Study TVP-1012/111 did not involve concomitant tyramine administration. No information was provided in the Safety Update, the study report or the subject's case report form regarding the tyramine content of her recent diet. Her prior study blood pressure measurements were normotensive, with standing measurements of 120/85 (Baseline), 120/80 (Week 1), 120/80 (Week 2), and 120/85 (Week 3). The subject's previously reported adverse events included headache, nausea and vomiting while receiving rasagiline 10 mg.

Subjects with Renal or Hepatic Impairment: Teva states that no SAEs were reported for either of these cohorts.

4.5.4 Clinical Pharmacology: Discontinuations for Adverse Events

Phase I/Healthy Volunteers: The sponsor states that five subjects in each of the rasagiline (3.2%) and naive¹⁹ (7.7%) groups discontinued the study prematurely. Termination reason "due to adverse experience" was recorded only for one (0.6%) rasagiline-treated subject (Phase I Safety Update 6.11). Teva reported that this one subject (TVP-1012/421 #16) discontinued prematurely due to rhinopharyngitis, which developed eight days after receiving a single dose of rasagiline 2 mg (Phase I/II Safety Update 7.1.6.1).

Phase II/LD-Treated PD Patients: Teva states that six subjects in this cohort discontinued prematurely due to AE and one discontinued for another reason. Three of these seven subjects were receiving rasagiline 1 mg, while the remaining four received 2 mg/day or more. AEs leading to discontinuation for the three 1mg subjects included: fall (occurring on study drug day 16), syncope (occurring on study drug day 14), and an episode of high blood pressure/tachycardia (occurring on study drug day 23). Teva notes that the latter two patients had a history of syncope and labile blood pressure, respectively, prior to treatment with rasagiline (Phase 1 Safety Update 7.1.6.2)

¹⁹ The sponsor states that naive subjects were those never exposed to rasagiline throughout the study, or subjects who were switched from placebo to rasagiline.

The AEs leading to discontinuation in the four subjects treated with rasagiline 2 mg or more are summarized below:

TVP-1012/111 #801 was withdrawn on study day 37 after multiple complaints of weakness, falling, vertigo and postural hypotension after receiving rasagiline 5 mg, 10 mg and one dose of 2 mg.

TVP-1012/111 #803: This subject's narrative is provided in the SAE section above.

TVP-1012/111 #808: This subject's narrative is provided in the SAE section above.

TVP-1012/132 #206, dosed with rasagiline 2 mg/day, discontinued the study following a hypertensive reaction associated with a tyramine challenge of 25 mg and 50 mg under fasting conditions. She is classified as withdrawing prematurely due to AE.

Subjects with Renal or Hepatic Impairment: Teva reports that the only discontinuation in the hepatic impairment cohort was due to symptoms of alcohol withdrawal. The sponsor's summary of the renal impairment cohort did not mention any discontinuations due to AE (Phase 1 Safety Update 7.1.7).

4.5.5 Clinical Pharmacology: Treatment Emergent Adverse Events

Teva notes that the integrated safety analysis of Phase I/Clinical Pharmacology studies included data from pharmacodynamic interaction studies, during which subjects were exposed to theophylline or high doses of tyramine with and without rasagiline. The sponsor states that although symptoms precipitated by tyramine administration were included in the tabulated AE data, they were also considered endpoints in the pharmacodynamic tyramine challenge study, and therefore expected to occur (to some degree) (Phase I/II Safety Update 7).

Phase I/Healthy Volunteers: Teva states that adverse events (AEs) were reported by 49% of rasagiline subjects and 77% of placebo subjects (Phase I/II Safety Update Post-Text Table 37). AEs occurring in more than 2% of subjects and more frequent than in naïve subjects are summarized in the table below:

FDA Table 17: Common Adverse Events in the Phase I/Healthy Volunteer Cohort in Descending Order of Difference of Rasagiline over Naïve Subjects (Sponsor Table 13, Phase I/II Safety Update)

Rasagiline ISS: Phase I/Clinical Pharmacology Studies (Healthy Volunteers)	Rasagiline (N=156)		Naive (N=65)		Rasagiline vs. Naive
	No. of Subjects	% of Subjects	No. of Subjects	% of Subjects	
MYALGIA	7	4.5	2	3.1	1.4
FLATULENCE	9	5.8	3	4.6	1.2
DYSPEPSIA	4	2.6	1	1.5	1.0
SOMNOLENCE	4	2.6	1	1.5	1.0
EPISTAXIS	4	2.6	1	1.5	1.0
RASH	4	2.6	1	1.5	1.0

Teva asserts that because of the potential cardiovascular effects of MAO inhibitors, special attention was paid to cardiovascular AEs. The sponsor reports that the only

cardiovascular AEs that occurred without tyramine or theophylline were two syncopal events: one reported several days after rasagiline was discontinued, and one described as “mild AE of vasovagal reflex” (Phase I/II Safety Update, 7.1.3.1).

Phase II/LD-Treated PD Patients: Teva states AEs were generally similar or slightly more frequent in placebo (73.9%) than in the rasagiline 1 mg (53.6%) group. Back pain (rasagiline 1 mg 14.3%, 4/28; placebo 4.3%, 1/23, dizziness (rasagiline 14.3%, 4/28; placebo 4.3%, 0/23, abdominal pain (rasagiline 7.1%, 2/28; placebo n=0), flu syndrome (rasagiline 3.6%, 1/28; placebo n=0), and hypertension (rasagiline 3.6%, 1/28; placebo n=0) were the AEs with the largest difference in incidence of rasagiline 1 mg compared to placebo (Phase I/II Safety Update, Table 14).

The sponsor reports that cardiovascular AEs appeared to demonstrate a dose-response relationship), as shown in the table below (Phase I/II Safety Update Table 12). The cardiovascular AEs reported for this cohort included the following:

FDA Table 18: Number and Percent of Levodopa-Treated Phase I/II Subjects with Cardiovascular Adverse Events (Adapted from Sponsor Post-Text Table 42, Phase I/II Safety Update)

	Rasagiline 0.5 mg (N=21)		Rasagiline 1 mg (N=28)		Rasagiline 2 mg (N=28)		Rasagiline >2mg (N=5)		Placebo (N=23)	
	# Pts.	%	# Pts.	%	# Pts.	%	# Pts.	%	# Pts.	%
All	1	4.8	3	10.7	5	17.9	3	60	2	8.7
ECG Abnormal	1	4.3
Hypertension	.	.	1	3.6	2	7.1	2	40	.	.
Hypotension	2	7.1
PVD ²⁰	1	3.61
Postural Hypotension	1	4.8	1	3.6	1	3.6	1	20	1	4.3
Syncope	.	.	1	3.6	.	.	1	20	1	4.3
Tachycardia	.	.	1	3.6

Reviewer comment: Given that cardiovascular adverse events as a whole is a broad and heterogeneous category, and given the small number of subjects affected within the pool of Phase I/II studies, conclusions on the relationship between cardiovascular adverse events and dose from the data in the table above should be made with caution.

Teva states that in a dose escalation study in patients on chronic levodopa therapy treated with rasagiline 10 mg (Study TVP-1012/111), there were three reports of cardiovascular side effects (including hypertension and postural hypotension) which resolved following treatment discontinuation (ISS 12.6). All three of the cardiovascular adverse events were

²⁰ Peripheral vascular disease

reported while the subjects were being treated with rasagiline 10 mg (TVP-1012/111 Study Report 7.2.2.2).

Teva reports that two rasagiline-treated subjects and one placebo-treated subject experienced anemia. Narratives for the rasagiline subjects are summarized below: **TVP-1012/132 #107** (rasagiline 1 mg) entered the study with baseline anemia (hemoglobin [Hgb] 10.1 g/dL) and lymphopenia (WBC 3.92×10^3). He completed the study with similar values (Hgb 9.7 g/dL, WBC 4.4×10^3). **TVP-1012/132 #202** (rasagiline 2 mg) experienced an AE of anemia on study drug day 26. He entered the study with a hemoglobin of 12.5 g/dL, which decreased to 10.2 g/dL and then rose to 11.5 g/dL while on rasagiline.

Subjects with Renal or Hepatic Impairment: AEs were reported by 66.7% (6/9) of subjects with mildly impaired hepatic function, and 50% (4/8) of subjects with moderately impaired hepatic function. AEs reported by subjects with hepatic impairment included constipation (n=4), asthenia (n=2), dizziness (n=1), headache (n=1) and diarrhea (n=1) (Phase I Safety Update Post-Text Table 47).

In the renal impairment cohort, AEs were reported in 50% (4/8) of subjects with normal renal function, 50% (4/8) of subjects with mild renal impairment and 62.5% (5/8) of subjects of moderately impaired renal function. AEs reported by subjects with renal impairment included diarrhea (n=3), flatulence (n=3), myalgia (n=2), constipation (n=1), and dizziness (n=1).

I reviewed sponsor tables summarizing AEs from for the four cohorts summarized above. I found no events suggestive of renal failure, hepatic failure, rhabdomyolysis, pancreatitis, agranulocytosis, or serious skin reactions.

4.5.6 Clinical Pharmacology: Laboratory Data

Phase I/Healthy Volunteers: The sponsor states that there were no potentially clinically significant (PCS) shifts in biochemistry laboratory values from baseline to last observed value during the Phase I studies (Phase I Safety Update 7.2.1.1). Analyses comparing baseline to maximum values were not provided. Teva states that no AEs related to abnormal biochemistry were reported.

Phase II/LD-Treated PD Patients: The sponsor states that an AE of “liver function tests abnormal” was noted for a subject who entered the study with alkaline phosphatase of 426 (range 35-115 U/L) that subsequently decreased on rasagiline 1 mg to 197 U/L. Six rasagiline-treated subjects had transaminase elevations one to three units above the upper limit of normal (Phase I Safety Update 7.2.1.2). One AE of hyperglycemia was recorded for a subject who entered the study with glucose 211 (study day one) which subsequently normalized on rasagiline 2 mg. Teva reports that no clinically significant trends were observed during urinalyses testing.²¹

²¹ I reviewed the sponsor’s tables presenting urinalysis data for the Phase I/II cohorts and corroborated that no clinically significant trends were apparent.

During hematology laboratory monitoring, one subject experienced a decrease in platelet count from $205 \times 10^3/\mu\text{L}$ two weeks after discontinuing rasagiline (due to hypertension and tachycardia) to $86 \times 10^3/\mu\text{L}$ six weeks after discontinuation. Two subjects with anemia are summarized in Section 4.5.5 above. Teva states no notable difference between placebo and rasagiline 1 mg were seen in shift analysis for urinalysis (Phase I Safety Update Post-Text Table 58).

Teva did not provide a summary analysis of laboratory data for subjects with hepatic and renal impairment.

4.5.7 Clinical Pharmacology: Vital Sign Data

Phase I/Healthy Volunteers: Teva states that naïve subjects had a similar or higher incidence of post-baseline PCS vital signs measurements for all parameters when compared to rasagiline-treated subject (Phase I Safety Update 7.3.3).

Phase II/LD-Treated PD Patients: Teva reports that the effect of rasagiline 1 mg on vital signs was generally similar to that of placebo. The exception to this was a trend toward higher mean change in pulse for higher doses of rasagiline (> 2 mg: mean increase of 6.8 bpm from baseline to LOV) over placebo (mean increase of 0.9 bpm), but no consistent effect on BP was observed.

Teva did not present vital sign summaries for the Phase I subjects with renal or hepatic impairment.

4.5.8 Clinical Pharmacology: ECG Data

The sponsor assessed ECGs through shift analysis (normal to abnormal, or vice versa) from baseline to LOV. The nature of the abnormalities were not specified.

Phase I/Healthy Volunteers: Teva notes that the five (20%) subjects who shifted from normal to abnormal ECGs were all participants in a study in which concomitant theophylline was given (Phase I/II Safety Update 7.4.1).

Reviewer comment: *To better assess whether these ECG abnormalities are potentially associated with theophylline, a question has been forwarded to Teva inquiring as to the specific nature of the ECG abnormalities.*

Phase II/LD-Treated PD Patients: Teva reports that a similar number of subjects (one from each treatment group) shifted from normal to abnormal ECG in the rasagiline 0.5 mg, 1 mg and placebo groups (Phase I/II Safety Update 7.4.2).

Reviewer comment: *Data on QT interval data (QTc) for this cohort has also been requested from the sponsor.*

Teva did not provide summaries of any ECG data for Phase I subjects with renal or hepatic impairment.

4.6 Phase II/III Studies

4.6.1 Deaths

Reviewer comment: This review generally presents data for the two placebo-controlled cohorts (Cohort 1 and 2) before data on Cohort 9 (all PD subjects exposed to rasagiline). However, in this section I begin with data from Cohort 9 as an overview, and subsequently present Cohort 1 and 2.

Cohort 9: All PD Patients Exposed to Rasagiline

Teva reports that during the entire rasagiline clinical program (data accumulated until November 30, 2003) a total of 32 participants died (ISS 120 Day Update 5.5.1.1). These deaths included: twenty-one subjects treated with rasagiline, five subjects treated with entacapone, and six subjects treated with placebo. All of the deaths occurred in subjects with PD, with the exception of one rasagiline-treated participant with Alzheimer's disease (TVP-1012/311 #349). The risk of death for PD patients within the entire rasagiline development program was 1.5% for those on rasagiline (20/1360), 2.6% for those on entacapone (6/227) and 0.9% for those on placebo (5/562) (ISS 120 Day Update 5.5.1.1).

Deaths in rasagiline-treated subjects are summarized in the table immediately below. I reviewed all death narratives and related data, and provide condensed versions of the sponsor's death narratives for rasagiline-treated subjects in the Attachments of this review.

FDA Table 19: Deaths Among Rasagiline-Treated Participants (adapted from Sponsor Table 31, ISS 120 Day Update)

Abbreviations: CVA: Cerebrovascular accident, IHD: Ischemic Heart Disease, CAD: Coronary Artery Disease, TIA: Transient Ischemic Attack, SAE: Serious Adverse Event

Study/Pt. ID	Age/ Sex	Comment	Days on Drug to Onset	Dose (mg/da y)
<i>Cerebrovascular Accidents</i>				
PRESTO #40	73/M	Brainstem stroke, history of hypertension, vital signs normal during study	99	1
PRESTO #93	77/M	CVA complicated by pneumonia, history of hypertension, normal vital	158	0.5

		signs during study		
LARGO Ext. ²² #15826	76/M	No prior history of hypertension, although elevated blood pressure during study, history of IHD	46	1
TEMPO Ext. ²³ #435	77/F	History of hypertension, CAD, smoking, prior TIA and CVA	1264	1
TEMPO Ext. #150	61/F	Non-hemorrhagic CVA with seizures, history of hypertension, normal vital signs during study	1551	1
PRESTO Open-Label Ext. ²⁴ #639	52/F	Hemorrhagic CVA, complicated by pneumonia; No history of hypertension	495	1
<i>Sudden Death</i>				
PRESTO Open-Label Ext. #125	68/M	Found unconscious while snorkeling, severe CAD on autopsy	588	1
TVP-1012/311 ²⁵ #349	77/M	Died in his sleep; History of Alzheimer's disease and heavy smoking	35	3
<i>Ruptured Aneurysm</i>				
TEMPO Ext. #68	75/M	Ruptured thoracic aneurysm, history of hypertension and high cholesterol	1410	1
<i>Pneumonia</i>				
LARGO #16415	71/F	Aspiration pneumonia, history of diabetes	144	1
PRESTO Ext. ²⁶ #601	80/F	Pneumonia, then pulmonary embolism and chronic respiratory failure	89	0.5
<i>Cancer</i>				
LARGO Ext. ²⁷ #15602	64/M	Gastric lymphoma	401	1
TEMPO Ext. #164	74/M	Recurrent metastatic melanoma	673	1
LARGO Ext. #50110	77/M	Carcinoma of the prostate	299	1
TEMPO Ext. #99	78/M	Carcinoma of the colon	1498	1
<i>Accidental</i>				
PRESTO Open-Label Ext. #555	70/M	Carbon monoxide poisoning from use of generator in home during storm	701	0.5

²² TVP-1012/123

²³ TVP-1012/233

²⁴ TVP-1012/135A

²⁵ Study TVP-1012/311 was a randomized, double-blind study of rasagiline up to 4 mg in persons with Alzheimer's disease, and without Parkinson's disease.

²⁶ TVP-1012/135

<i>Complex</i>				
LARGO #16006	70/M	Bowel obstruction, surgery, sepsis, pneumonia, pulmonary embolism	113	1
PRESTO Open-Label Ext. #378	76/F	Urinary tract infection, pneumonia, cardiac arrest	868	1
<i>Unknown</i>				
TEMPO Ext. #95	70/F	Found dead in overheated apartment, no history of heart disease	135	2
TVP-1012/113 #1021	63/M	Hospitalized for paranoid disorder, rasagiline discontinued; died at home five months later of unknown cause	>1461	1
TEMPO Ext. #332	76/M	SAE of coronary bypass surgery, post-op atrial fibrillation, stroke; withdrawn from study four months later due to difficulty keeping appointments; died five months later of unknown cause	>882	1

Reviewer comment: *In the preceding table, the division of deaths into the various categories was taken from the original sponsor table. For subjects whose death was both relatively sudden and for which the cause was uncertain, the sponsor criteria for classifying them as either “Sudden Death” (PRESTO Open-Label Ext. #125, TVP-1012/311#349) or “Unknown” (TEMPO Ext. #95) was not specified.*

Information on the deaths of the six entacapone-treated subjects is summarized in the following table. One participant (LARGO Ext. #90107) also received rasagiline on a compassionate use basis:

FDA Table 20: Deaths among Six Entacapone-Treated Patients in the Rasagiline Development Program (Adapted from Sponsor ISS Table 33)

LARGO #16305	61 year-old woman who died suddenly one day after entering the study, following her second dose of entacapone
LARGO #15407	67 year-old woman who died of a pulmonary embolism following surgery for a broken hip
LARGO #15418	82 year-old man who died four days into the study of pneumonia complicated by renal failure
LARGO Ext. #90107	70 year-old man diagnosed with recurrent metastatic colon cancer while receiving entacapone as part of LARGO. He began compassionate use of rasagiline (1 mg) for 14 months prior to his death from progressive metastatic disease
LARGO Ext. #41607	78 year-old man died of cardiopulmonary failure following a complicated illness: congestive heart failure, diarrhea, and hypovolemia complicated by pneumonia, decubitus ulcers and anemia
LARGO Ext. #15511	62 year-old man died following acute shortness of breath 200 days into the study

Causes of deaths for the five placebo-treated participants are given in the table below.

FDA Table 21: Deaths among Placebo Subjects in the Rasagiline Development Program (Adapted from Sponsor ISS Table 32)

LARGO #15719	71 year-old man deceased following ischemic vascular insufficiency complicated by pneumonia and respiratory failure
LARGO #16030	60 year-old woman who died in her sleep after complaining of respiratory difficulty the day prior; no reported cardiac history
LARGO #90113	78 year-old man deceased from an aortic dissection
LARGO Screening # 141401	72 year-old woman who died from a myocardial infarction during the run-in phase of the study
LARGO #15409	67 year-old man who committed suicide by hanging

Reviewer comment: As person-time and median duration of treatment were similar between treatment arms within the three pivotal trials, as well as between the rasagiline (1 mg) and placebo groups within the two placebo-controlled cohorts, the data below will be primarily presented as risks (percentages), and not rates.

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

No deaths occurred during the two studies (the placebo-controlled phase of TEMPO [TVP-1012/232] and TVP-1012/231) comprising Cohort 1 (ISS 6.7.1.1).

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

Of the 21 rasagiline-treated participants who died throughout the development program, four were participants in the placebo-controlled portions of LARGO or PRESTO, and therefore members of Cohort 2. Three entacapone-treated and four placebo-treated participants²⁸ in LARGO or PRESTO (described in the tables above) also died.

FDA Table 22: Number and Percentage of Deaths in Cohort 2 by Treatment Group (Sponsor ISS Table 50)

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²⁸ LARGO participant # 141401 was excluded from this calculation as her death from an acute myocardial infarction occurred during the run-in phase of the study.

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)		Placebo (N=388)	
		Death		Death	
		No. of Patients	% of Patients	No. of Patients	% of Patients
-ALL	-ALL	3	0.8	4	1.0
BODY AS A WHOLE	-ALL	.	.	2	0.5
	SUDDEN DEATH	.	.	1	0.3
	SUICIDE ATTEMPT	.	.	1	0.3
CARDIOVASCULAR SYSTEM	-ALL	2	0.5	2	0.5
	AORTIC DISSECTION	.	.	1	0.3
	CEREBROVASCULAR ACCIDENT	1	0.3	.	.
	CEREBROVASCULAR DISORDER	.	.	1	0.3
RESPIRATORY SYSTEM	PULMONARY EMBOLUS	1	0.3	.	.
	-ALL	1	0.3	2	0.5
	DYSPNEA	.	.	1	0.3
	PNEUMONIA	.	.	1	0.3
	RESPIRATORY DISORDER	1	0.3	.	.

Cohort 2 Deaths by Study

For LARGO, two patients from the rasagiline treatment group (0.9%, 2.6 per 100 person-years), three patients from the entacapone treatment group (1.3%, 4.0 per 100 person-years), and four patients from the placebo treatment group (1.7%, 5.4 per 100 person-years) died after randomization and the initiation of the study drug (LARGO study report, 12.2.1.3).

For PRESTO, one subject died in each of the rasagiline 0.5 mg (0.6%, 1.3 per 100 person-years) and 1.0 mg (0.7%, 1.4 per 100 person-years) groups. Both died from cerebrovascular accidents (PRESTO study report, 10.2.3). No patients died in the placebo group.

Deaths in Cohort 3 through 8

Apart from the four deaths in Cohort 2, the 28 remaining deaths in the rasagiline development program occurred during the extension trials. Summaries of these deaths are provided in Table 14 above and in Attachment 9.2. Given the small number of deaths per cohort, lack of placebo-control and overlap with Cohort 9 (all PD patients treated with rasagiline), I did not address deaths in Cohorts 3 through 8 on an individual cohort basis.

Reviewer comment: *The relatively small number of deaths in the rasagiline development program precluded more detailed analysis, including meaningful cause-specific mortality within the placebo-controlled cohorts and dose-response relationships. On general review, however, causes of death were typical of those expected in an older patient population. No apparent clusters were seen, with the possible exception of cerebrovascular accidents, discussed below.*

Cerebrovascular Accidents

Overall death rates for participants treated with rasagiline, placebo or entacapone were similar. However, throughout the development program more rasagiline-treated participants (n=6) died of confirmed cerebrovascular accidents than placebo- and entacapone-treated participants (n=1). For PRESTO, two deaths from CVAs (2/313, or 0.6%) occurred in the rasagiline treatment groups, compared to no deaths from CVA in the placebo-treatment group (As noted above, the person-time and median treatment duration were very similar for the PRESTO treatment and placebo arms, allowing comparison by risk.) The remainder of the stroke deaths occurred in extension studies without placebo control. Although the number of CVA deaths was small and therefore especially susceptible to variation by chance, the elevated rate is of concern due to possibility of tyramine reactions and hypertensive crisis. I did not find specific evidence of tyramine-reaction symptoms in the death narratives, although there were several deaths from unknown causes. The narrative for subject TVP-1012/311 #349 (an Alzheimer's disease patient receiving rasagiline 3 mg/day who died unexpectedly in his sleep) stated that family members believed his last meal to have been of low tyramine content. This was the only narrative containing such information. Of note, the risk of stroke as a SAE for rasagiline and placebo groups in Cohort 2 was similar: rasagiline (n=2, 0.5%) and placebo (n=1, 0.3 %) (ISS Table Post-Text Table 85 and 86). No CVAs were reported as a SAE in either the rasagiline- or placebo-treated subjects in Cohort 1.

No deaths among rasagiline-treated subjects were attributed to hepatic failure, renal failure, serious skin reactions, hematologic dyscrasias, pancreatitis, or rhabdomyolysis.²⁹ One death occurred from melanoma, and the occurrence of melanoma within the rasagiline development program is discussed in detail in section 4.7 of this review.

As rasagiline has not yet been marketed outside the United States, there are no reports of deaths from the post-marketing period.

4.6.2 Serious Adverse Events

Teva reports that serious adverse events (SAEs) occurred in 19% of all subjects exposed to rasagiline (ISS 120-day update 5.5.2.5). SAE rates stratified by the nine analysis cohorts within the ISS are summarized below:

FDA Table 23: Summary of SAEs for Rasagiline ISS Analysis Cohorts

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²⁹ Two cases of rhabdomyolysis occurring as serious adverse events (SAEs) are described in Section 4.6.2 of this review.

Cohort	# SAEs	# Total AEs	SAEs as % of Total AEs	% Cohort Subjects Reporting an SAE	SAE Reports per 100 PYs
1. Placebo-controlled rasagiline monotherapy (Rasagiline 1 mg only)³⁰	12	486	2.7	8.0	18.7
2. Placebo-controlled rasagiline as LD³¹ adjunct (Rasagiline 1 mg only)	53	916	5.7	13.9	36.1
3. Rasagiline Monotherapy – Any Treatment Duration	70	3083	2.3	18.6	17.4
4. Rasagiline Monotherapy – Long Term Treatment	98	2676	3.7	21.4	14.2
5. Rasagiline with LD in Non- Fluctuating Patients – Any Treatment Duration	91	1435	6.2	26.2	27.4
6. Rasagiline with LD in Non- Fluctuating Patients – Long Term Treatment	73	1210	6.0	34.3	23.9
7. Rasagiline with LD in Fluctuating Patients – Any Treatment Duration	163	2247	7.3	14.3	28.0
8. Rasagiline with LD in Fluctuating Patients – Long Term Treatment	43	929	4.6	11.2	12.3
9. All PD Patients Ever Exposed to Rasagiline	502	904	5.6	19.0	24.9

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor states that in Cohort 1 SAEs occurred in six subjects (4.0%) in the rasagiline 1 mg group, nine subjects (6.2%) in the rasagiline 2 mg group and four subjects (2.6%) in the placebo group , all in the TEMPO study (see table below).

FDA Table 24: Number and Percent of Cohort 1 Members Experiencing SAEs by Treatment Group (Sponsor ISS Post-Text Table 85)

³⁰ For this table, only data from the rasagiline 1 mg group of the placebo-controlled cohorts was used. SAEs stratified by rasagiline dose and compared to rates in the placebo group are presented below.

³¹ LD: Levodopa.

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		All Rasagiline Doses (N=295)			Rasagiline 1 mg (N=149)			Rasagiline 2 mg (N=140)			Placebo (N=151)		
		Serious			Serious			Serious			Serious		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
-ALL	-ALL	31	15	5.1	12	6	4.0	19	9	6.2	6	4	2.6
BODY AS A WHOLE	-ALL	6	5	1.7	2	1	0.7	4	4	2.7	1	1	0.7
	ABDOMINAL PAIN	2	2	0.7	-	-	-	2	2	1.4	-	-	-
	CHEST PAIN	1	1	0.3	-	-	-	1	1	0.7	1	1	0.7
	DRUG INTERACTION	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	NEOPLASM	2	1	0.3	2	1	0.7	-	-	-	-	-	-
CARDIOVASCULAR SYSTEM	-ALL	9	5	1.7	5	4	2.7	1	1	0.7	-	-	-
	ANGINA PECTORIS	3	3	1.0	2	2	1.3	1	1	0.7	-	-	-
	ATRIAL FIBRILLATION	2	1	0.3	2	1	0.7	-	-	-	-	-	-
	HEART ARREST	1	1	0.3	1	1	0.7	-	-	-	-	-	-
	MYOCARDIAL INFARCT	1	1	0.3	1	1	0.7	-	-	-	-	-	-
	THROMBOSIS	1	1	0.3	1	1	0.7	-	-	-	-	-	-
	VASCULAR DISORDER	1	1	0.3	1	1	0.7	-	-	-	-	-	-
DIGESTIVE SYSTEM	-ALL	6	3	1.0	1	1	0.7	5	2	1.4	1	1	0.7
	CHOLELITHIASIS	-	-	-	-	-	-	-	-	-	1	1	0.7
	COLITIS	2	2	0.7	1	1	0.7	1	1	0.7	-	-	-
	CONSTIPATION	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	INTESTINAL OBSTRUCTION	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	NAUSEA	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	VOMITING	1	1	0.3	-	-	-	1	1	0.7	-	-	-
NERVOUS SYSTEM	-ALL	5	1	0.3	-	-	-	5	1	0.7	2	2	1.3
	CONFUSION	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	DEPRESSION	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	DIZZINESS	1	1	0.3	-	-	-	1	1	0.7	1	1	0.7
	DYSARTHRIA	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	SOMNOLENCE	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	TREMOR	-	-	-	-	-	-	-	-	-	1	1	0.7
RESPIRATORY SYSTEM	-ALL	-	-	-	-	-	-	-	-	-	1	1	0.7
	DYSPNEA	-	-	-	-	-	-	-	-	-	1	1	0.7
SKIN AND APPENDAGES	-ALL	4	3	1.0	1	1	0.7	3	2	1.4	-	-	-
	SKIN CARCINOMA	2	1	0.3	-	-	-	2	1	0.7	-	-	-
	SKIN MELANOMA	1	1	0.3	-	-	-	1	1	0.7	-	-	-
	SWEATING	1	1	0.3	1	1	0.7	-	-	-	-	-	-
UROGENITAL SYSTEM	-ALL	1	1	0.3	-	-	-	1	1	0.7	1	1	0.7
	CYSTOCELLE	-	-	-	-	-	-	-	-	-	1	1	0.7
	PROSTATIC CARCINOMA	1	1	0.3	-	-	-	1	1	0.7	-	-	-

Of the six SAEs in the rasagiline 1 mg treatment group, four were cardiovascular in nature (summarized below). CV SAEs for Cohort 1 occurred in 2.7 % of subjects treated with rasagiline 1 mg (n=4, 12 reports/100 PYs), 0.7 % of subjects treated with rasagiline 2 mg (n=1, 1.6 reports/100 PYs), and 1.7% of all subjects treated with rasagiline at either of the two doses (n=5, 7.1 reports/100 PYs). No patients reported a CV SAE in the Cohort 1 placebo group.

TEMPO #148: This 72 year-old man with a history of myocardial infarction (MI), cardiac catheterization and diabetes developed anteroseptal MI two months after study entry, followed by an angioplasty with stent placement.

TEMPO #179: This 72 year-old woman underwent elective repair of a longstanding abdominal aortic aneurysm which was complicated by an intraoperative cardiac arrest/myocardial infarction, deep venous thrombosis, and residual foot drop.

TEMPO #286: This 66 year-old man with a history of atypical chest pain and hyperlipidemia underwent coronary artery bypass surgery five months after study entry. He subsequently developed duodenal gastritis during his hospitalization.

TEMPO #616: This 74 year-old man developed new onset atrial fibrillation on study day 183.

Cardiovascular SAEs from the rasagiline 2 mg treatment group are described below:

TEMPO #146: A 68 year-old man with a history of myocardial infarction, smoking, and hyperlipidemia experienced severe angina pectoris two weeks after study entry. The subject was treated medically with nifedipine, atorvastatin, nitroglycerin patch and isosorbide mononitrate, and rasagiline was suspended. Teva states the subject terminated due to need worsening depression and the need for medication (fluoxetine) that was disallowed by the study protocol.

Among the other SAEs for rasagiline-treated Cohort 1 members, Teva reports that TEMPO #408 had an ovarian teratoma removed, TEMPO #120 experienced a recurrence of previously diagnosed diverticulitis and TEMPO # 139 was diagnosed with prostate cancer after 81 days of receiving rasagiline 2 mg (ISS 6.7.2.1.1).

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

Teva states that SAEs were reported for 30 patients on rasagiline 1 mg (7.9%) and 31 patients on placebo (8.0%). The sponsor notes that although the incidence of SAEs is more than double that of Cohort 1, these participants were generally more complex medically, with a longer history of PD and chronic levodopa treatment (ISS 6.7.2.1.2). The sponsor states this is supported by the similar AE rates for the rasagiline and placebo subjects. The sponsor table summarizing SAEs within Cohort 2 is included in Attachment 9.3 of this review.

Teva notes that the frequency of SAEs in the rasagiline-treated participants was similar to or lower than the placebo group for almost all categories, with the exception of Body as a Whole (rasagiline 3.4% vs. placebo 2.1%). SAEs in which the occurrence in the rasagiline 1 mg group differed from the placebo group by more than one patient included: arrhythmia (one subject with tachy-bradycardia, another with sick sinus syndrome), postural hypotension, pulmonary embolus and intestinal obstruction (each with two rasagiline subjects each compared to none for placebo) (ISS 6.7.2.1.2).

AV Block

In the table summarizing SAEs in Cohort 2 (Attachment 9.3 of this review), there is one report each of SAEs for AV block first degree, AV block second degree and AV block complete in rasagiline-treated subjects, compared to none in the placebo groups. To investigate whether these AEs occurred in a single or multiple subjects, I searched the sponsor AE datafile for ISS Cohort 9 (AE_C9) for the COSTART term AV Block. This yielded eight subjects who experienced eleven adverse events of AV block. Four subjects were participants in the Cohort 2 study LARGO, three were participants in the Cohort 2 study PRESTO, and one was a participant in the TEMPO Extension trial.

Of the three cases of AV block in Cohort 2 members that were classified as serious (and noted in the sponsor table), one subject (LARGO #41002) experienced both the SAES of first and second degree AE block, while a second subject (LARGO #16429) experienced complete AV block. Narratives for the two subjects are given below:

LARGO #41002: This 71 year-old woman received rasagiline 1 mg/day, and was noted to have a past medical history of ischemic heart disease, hypertension and hypercholesterolemia. Ten days after she had discontinued rasagiline following normal completion of the placebo-controlled phase of the study, she experienced retrosternal pressure and dyspnea. An outpatient ECG demonstrated transient first and second degree AV block, and she was admitted to the hospital. She was stated to have been discharged and recovered to her baseline status. There was no indication in the sponsor narrative of subsequent episodes or pacemaker implantation.

LARGO #16429: This 75 year-old woman with a history of hypertension experienced dyspnea approximately two weeks after beginning rasagiline 1 mg/day. An echocardiogram revealed severe mitral insufficiency, mild aortic insufficiency and moderate tricuspid insufficiency. On study drug day 59, she experienced dyspnea and orthopnea. Subsequent Holter monitoring revealed first degree AV block and two episodes of complete AV block. The study drug was discontinued (study drug day 64), and she was admitted to the hospital for further evaluation the following day. She subsequently received a pacemaker and was treated with amiodarone for tachycardia-bradycardia syndrome. Her family reported her to be in generally good health following her discharge, and no further cardiac events were noted in the narrative.

Cohort 3: Rasagiline Monotherapy – Any Treatment Duration

Teva notes that in Cohort 3, cardiovascular SAEs were the most commonly reported (6 reports/100 PYs, compared to 7.1 reports/100 PYs for all rasagiline-treated subjects in Cohort 1), followed by Body as a Whole (3.2 reports/100 PYs), digestive system (2.0 reports/100 PYs) and skin/appendages (1.6 reports/100 PYs). Combining SAEs associated with myocardial ischemic events (angina, coronary artery disorder, coronary occlusion and myocardial infarction) yielded 2.4 reports/100 PYs, followed by atrial fibrillation with 1.1 reports/100 PYs (ISS 6.7.2.2.1). Teva notes that the most common non-cardiovascular SAE was prostatic carcinoma (0.8 reports/100 PYs)³². Occurring with the same time-adjusted frequency (0.7 reports/100 PYs) was skin carcinoma³³, skin melanoma,³⁴ joint disorder (predominantly elective joint surgery) and chest pain (for which Teva notes that three out of the seven cases were classified as non-cardiac). Teva suggests this mix of AEs could be expected in an elderly population such as those enrolled in the rasagiline development program.

Cohort 4: Rasagiline Monotherapy – Long-Term Treatment

In this subset of Cohort 3, the sponsor reports that time-adjusted frequencies of SAEs remained stable or decreased somewhat in comparison to Cohort 3 overall (ISS 6.7.2.2.2). Teva therefore asserts that no effect on SAEs attributable to long-term rasagiline treatment was evident.

Reviewer comment: *In long-term treatment cohorts, the rates of common AEs may be affected by a “survivor bias,” in that subjects who tolerate rasagiline remain on the drug, contributing person-years without contributing additional AEs, while those with AEs had previously discontinued. It is therefore not unexpected that common AE rates in the long-term cohorts are lower than those for cohorts composed of subjects with any treatment duration.*

³² The occurrence of prostatic cancer within the rasagiline development program is discussed in more detail in Cohort 9 below.

³³ Teva treated skin melanomas and skin carcinomas as two separate AE categories. This is demonstrated by the AE dataset for Cohort 9, in which subjects with melanomas were coded as “skin melanoma” only, and were not additionally included among skin carcinomas. In addition, in some of the earlier tables (such as ISS Post-Text Table 86 for Cohort 2 SAEs) the number of cases of skin melanoma is greater than the number of cases of skin carcinoma, corroborating that skin melanoma is separate from, and not included within, the skin carcinoma category.

³⁴ Melanomas of the skin are discussed in detail in section 5.0 of this review.

*Cohort 5: Rasagiline as Levodopa Adjunct in Non-Fluctuating Patients - Any Treatment Duration*³⁵

Teva reports that the body system with the highest time-adjusted frequency of SAEs was the cardiovascular system (5.7 reports/100 PYs), followed by the digestive system, nervous system (4.8 reports/100 PYs each) and body as a whole (3.6 reports/100 PYs) (120 Day Update 5.5.2.1).

The sponsor states that the most common individual SAEs were accidental injury and syncope (4 [2.2%] patients each) followed by surgery and procedures, dehydration, arthralgia, depression, neuropathy, spinal stenosis, skin carcinoma, skin melanoma and gastrointestinal carcinoma (3 [1.6%] subjects each) (120 Day-Update 5.5.2.1).

Reviewer comment: *In the Cohort 9 AE dataset, four cases of gastrointestinal carcinoma were reported. All four were colon cancers, and from their verbatim description two appear to have been cancerous polyps found during routine screening.*

Teva notes that the majority of SAEs occurred in one or two subjects, and reports there was no consistent trend of individual SAEs associated with increased dopaminergic activity, such as nausea, vomiting, hallucinations, dyskinesia or postural hypotension.³⁶ SAEs of accidental injuries and syncope, including selected narratives, are discussed in more detail below (ISS 6.7.2.2.3).

Cohort 6: Rasagiline as Levodopa Adjunct in Non-Fluctuating Patients – Long-Term Treatment

Teva states that most SAEs in this long-term cohort remained stable or decreased in rate compared to Cohort 5 (ISS 6.7.2.2). The most common individual SAEs were neuropathy (1.9 reports/100 PYs), followed by skin carcinoma, accidental injury and AEs associated with coronary artery disease (each with 1.5 reports/100 PYs). When compared to the long-term rasagiline monotherapy Cohort 4, there was an overall increase in SAEs (14.2 to 23.9/100 PYs), most prominently for the digestive (0.9 to 4.4 reports/100 PYs) and nervous systems (0.6 to 4.9 reports/100 PYs). Teva notes there was a decrease in cardiovascular SAEs from the long term monotherapy Cohort 4 (5.1 reports/100 PYs) compared to long term levodopa adjunct Cohort 6 (3.4 reports/PYs).

Cohort 7: Active Treatment: Levodopa-Treated Fluctuating Patients - Any Treatment Duration

³⁵ This cohort represents the addition of levodopa to participants previously receiving rasagiline monotherapy in TEMPO.

³⁶ The sponsor cites ISS Post-Text Table 89, which lists rates and percentages for all SAEs in Cohort 5, as supporting the assertion that there was no trend of increased dopaminergic SAEs. I reviewed this table, and found one subject listed as experiencing an SAE of postural hypotension, and no subjects listed as experiencing SAEs of nausea, vomiting, hallucinations, or dyskinesia.

Teva states that the most frequent SAEs for Cohort 7 occurred in the following body systems: body as a whole (7.2 reports/100 PYs), the cardiovascular system (6.0 reports/100 PYs), the nervous system (5.7 reports/100 PYs) and the digestive system (2.7 reports/100 PYs). Specific SAEs reported most often, and in more than two (0.3%) patients, included: accidental injury (2.7 reports/100 PYs), hernia (1.0 reports/100 PYs) cerebrovascular accident, syncope, and skin melanoma (each with 0.9 reports/100 PYs), surgery and procedures, intestinal obstruction and extrapyramidal syndrome (each with 0.7 reports/100 PYs), and postural hypotension, bronchitis, arrhythmia, psychosis, and spinal stenosis (each with 0.5 reports/100 PYs)(120 Day Update 5.5.2.3). Of the 13 (2%) patients with accidental injury, five were associated with falls causing fractures or other injuries. These are discussed in more detail below.

Cohort 8: Active Treatment: Levodopa-Treated Fluctuating Patients – Long-Term Treatment

The sponsor states that in this long-term cohort the rate of AEs decreased considerably for postural hypotension (3.1 reports vs. 8.1/100 PYs in Cohort 7), increased slightly for hypotension (3.7 vs. 2.6 reports/100 PYs in Cohort 7) and remained stable for hypertension (2.6 vs. 2.7 reports/100 PYs) (120 Day Update 6.1.4). Teva states that the majority of SAEs in this cohort were reported only once (120 Day Update 5.5.2.4).

Cohort 9: All PD Patients Ever Exposed to Rasagiline

SAEs in Cohort 9 were most frequently reported for the cardiovascular system (6.9 reports/100 PYs), followed the Body as a Whole (4.2 reports/100PYs), the Nervous System (3.4 reports/100 PYs) and the Digestive System (3.1 reports/100 PYs).³⁷

The sponsor notes that SAEs in this cohort were reported most often for accidental injury (14 subjects, one report/100 PYs), angina pectoris (14 subjects, one report/100 PYs), spinal stenosis (usually surgical repair) and prostate cancer (8 patients each, 0.5 reports/100 PYs), atrial fibrillation (0.7 reports/100 PYs), cerebrovascular accident and syncope (0.5/100 PYs each)(120 Day Update 5.5.2.5).

Discussion of Selected SAEs

I reviewed the listing of all SAEs in Cohort 9, as well as the narratives and related information for all SAEs in the three pivotal trials (LARGO, PRESTO and TEMPO). I found no events suggestive of acute liver failure, pancreatitis, serious rash, blindness, agranulocytosis or aplastic anemia. I summarize selected SAEs of interest (due to more frequent occurrence or more serious potential safety concern) below:

Prostate Cancer

³⁷ The organ system rates were provided via correspondence with Teva (dated April 12,2004), following a request from the Safety Reviewer to clarify rates in ISS 6.7.2.2.7.

To further evaluate the occurrence of prostate cancer in the rasagiline development program, the crude prostate cancer rate for rasagiline was compared to that for other Parkinson's disease therapies in the table below.³⁸

FDA Table 25: Prostate Cancer in Parkinson's disease Development Programs

	Total Number of Subjects	Number of Cases of Prostate Cancer	Percent of Subjects with Prostate Cancer
Pramipexole	2621	7	0.3%
Ropinirole	2165	6	0.3%
Entacapone	1150	0	NA
Tolcapone	1740	8	0.5%
Rasagiline	1360	8	0.6%

Reviewer comment: *While the number of cases of prostate cancer in the rasagiline development is higher than that for other programs (and approximately twice as high as two of the other Parkinson's disease therapies), this is somewhat mitigated by the small number of cases and that the rate for rasagiline is similar to that for tolcapone.*

In addition, these development programs cover a considerable time period, with studies for pramipexole and ropinirole taking place approximately ten to fifteen years prior to the rasagiline development program. Detection rates for prostate cancer have increased during this time due to the development and initiation of screening. The lower rates during the development programs for the older medications may simply reflect this trend.

Rhabdomyolysis

PRESTO #58: A 77 year-old man with chronic renal insufficiency (study screening laboratory values of creatinine 2 mg/dL and BUN 41 mg/dL) was discovered lying on the floor of his home in a confused state by a family member. The subject was hospitalized, with laboratory values: creatinine 2.3 mg/dL, BUN 62 mg/dL. His CPK value was within normal limits (78 IU/L, with normal range of 61 to 224 IU/L) two days following the fall. An e-mail correspondence from the sponsor stated it was unclear why the investigator classified this subject as having rhabdomyolysis. He recovered to his baseline status, and discontinued the study after 145 days. His creatinine at his termination visit was 1.9 mg/dL.

PRESTO #628: A 61 year-old man was reported to have run out of his levodopa and attempted to compensate with additional doses of trihexyphenidyl. He developed a delirium (thought to be induced by the trihexyphenidyl overdose) fell, and was unable to rise. He was found to be dehydrated with laboratory evidence of rhabdomyolysis (CPK 9735 U/L). He recovered, but was discontinued from the study.

Syncope

³⁸ The information on prostate cancer within the table was taken from the FDA safety reviews of the respective therapies. As the organization of the safety reviews varied considerably and as the information was abstracted from review of the paper reports, with the exception of rasagiline the data these figures should be considered as approximations.

Sixteen participants in Cohort 9 (all PD patients exposed to rasagiline) experienced an SAE of syncope.

***Reviewer comment:** I reviewed the narratives for all syncopal episodes, and found them to be heterogeneous in nature. I have selected the five cases below as a sampling of this heterogeneity. Of note, the syncopal episodes generally occurred after extended periods of rasagiline treatment. The absence of a close temporal relationship between the syncopal episode and the initiation of rasagiline suggests etiologies other than rasagiline treatment, but does not completely rule out a role for rasagiline.*

TEMPO Ext.³⁹ #92: A 76 year-old man with a history of myocardial infarction experienced a syncopal episode after 1836 days of rasagiline treatment (initially 2 mg/day during the placebo-controlled trial, then 1 mg/day during open-label treatment). After an electrophysiology study revealed an inducible ventricular fibrillation, the subject underwent defibrillator implantation.

TEMPO Ext. #97: A 78 year-old man with a history of postural hypotension and prior syncope, was found in an unresponsive state by his wife on day 1652 of rasagiline treatment. Several minutes later he awoke confused, with no recollection of the incident. He was hospitalized for further evaluation, and was found to have multiple bruises and a concussion. His fludrocortisone, which the subject had been taking previously along with levodopa/carbidopa, pramipexole, sertraline and donepezil, was increased. He was discharged and reported not to have experienced a subsequent similar episode.

TEMPO Ext. #212: A 70 year-old woman fainted during a bowel movement on day 1596 of treatment with rasagiline. She was admitted to the hospital and diagnosed with a vasovagal episode due to dehydration. She recovered following treatment with IV fluids. Concomitant medications were valsartan, hydrochlorothiazide, calcitonin, mirtazapine, and carbidopa/levodopa.

TEMPO Ext. #434: A 74 year-old woman with a history of postural hypotension experienced increasingly frequent syncopal episodes over a two-month period, which began after 455 days of rasagiline therapy. On examination, the patient suffered severe postural hypotension and had a potassium level of 2.9. The patient denied any chest pain, palpitations, or shortness of breath, and cardiac monitoring showed no arrhythmias. A definitive cause of the episodes was not found, and the subject was discontinued from the study.

LARGO Ext. #16029: This 68 year-old woman with a history of hypertension and atrial fibrillation experienced a syncopal episode, resulting in mild head trauma, after seven months of rasagiline treatment. Her blood pressure was 70/40 mmHg. She was reported to have recovered fully.

Accidental Injury

Fourteen subjects in Cohort 9 (all PD patients exposed to rasagiline) reported an SAE of accidental injury. A number of these resulted in fractures or other orthopedic injuries, including costal fractures (LARGO Ext. #16022) and hip fracture (LARGO Ext. #16036, LARGO Ext. # 16016, LARGO Ext. #16017, LARGO Ext. # 16222, and PRESTO Ext.

³⁹ TVP-1012/233

#424). A number of other subjects were noted to experience frequent falls without more severe injuries (LARGO Ext. 15709, LARGO Ext. #50508).

Reviewer comment: For AEs in general, in Cohort 1, 8.1% of rasagiline-treated subjects (1 mg) experienced an AE of accidental injury, compared to 9.9% in the placebo group. For Cohort 2 accidental injury occurred in 8.2% of the rasagiline 1 mg group and 5.2% of the placebo group. Rates of accidental injuries as an SAE in the placebo-controlled cohorts were similar in the rasagiline and placebo groups.

Anemia

For all subjects treated with rasagiline (Cohort 9), anemia occurred in 1.7%, although it was classified as an SAE in only the following two participants:

PRESTO Ext. #42: This subject is summarized in more detail in the Discontinuations (Section 4.6.3) of this review. She was hospitalized for syndrome of inappropriate anti-diuretic hormone secretion (SIADH), and during the admission was found to be anemic.

LARGO Ext. #16210: This 62 year-old man was admitted to the hospital after 16 days of rasagiline treatment for malaise, weakness and two episodes of melena beginning five days earlier. Anemia (hematocrit 16%), leukocytosis ($18.1 \times 10^3/uL$) and hypokalemia (2.7 meq/L) were found on admission. The subject denied alcohol abuse, smoking or treatment with NSAIDs or corticosteroids. Endoscopy revealed a gastric ulcer. During the hospitalization, the patient was treated with hydration, omeprazole, ranitidine and transfusion of four units of red blood cells. The study drug was temporarily discontinued. His laboratory values had returned to normal range by a one-month follow-up visit.

4.6.3 Discontinuation for Adverse Events

Teva states that participants who terminated early due to AE were identified as follows: The coding for discontinuing subjects was searched for the termination reason "Due to AE." For these participants, all AEs which resulted in the action "Drug Stopped" were listed in tables summarizing early terminations (ISS 1.5.5.3). Subjects classified as discontinuing due to AE but for whom no specific AE could be pinpointed were also noted in the discussion of terminations due to AE, but were not included in the tabulations. Approximately 7% of all discontinuations due to AE fell into this latter category (ISS 120 Day Update 5.5.3). This issue is discussed further in the section on Cohort 9 below.

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor states that five patients on rasagiline 1 mg (7.8/100 PY), two patients on rasagiline 2 mg (3.2/100 PYs), and one patient on placebo (1.5/100 PY) discontinued from Cohort 1 due to AE (Clinical Overview 2.5.5.2.6). Teva notes that the majority of AEs leading to discontinuation were reported in only one patient, except for hallucinations which occurred in three rasagiline-treated patients (two receiving rasagiline 1 mg, one receiving 2 mg). Hallucinations are discussed in more detail below. The sponsor reports that an additional participant (TEMPO #179) on rasagiline 1 mg

terminated 49 days after study entry due to an unspecified AE, but as none of the AEs were marked as “Dose Stopped” this subject was not included in the count above.⁴⁰

FDA Table 26: Frequency and Incidence of AEs Resulting in Early Termination in Cohort 1 (Sponsor ISS Post-Text Table 94)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		Rasagiline 1 mg (N=149)			Rasagiline 2 mg (N=146)			Placebo (N=151)		
		No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients	No. of Reports	No. of Patients	% of Patients
-ALL	-ALL	9	5	3.4	2	2	1.4	1	1	0.7
BODY AS A WHOLE	-ALL	2	2	1.3	.	.	.	1	1	0.7
	ASTHENIA	1	1	0.7
	CHEST PAIN	1	1	0.7
	FLU SYNDROME	1	1	0.7
CARDIOVASCULAR SYSTEM	-ALL	2	2	1.3
	CEREBROVASCULAR ACCIDENT	1	1	0.7
	HYPERTENSION	1	1	0.7
NERVOUS SYSTEM	-ALL	4	2	1.3	2	2	1.4	.	.	.
	DIZZINESS	1	1	0.7
	HALLUCINATIONS	3	2	1.3	1	1	0.7	.	.	.
	PARESTHESIA	.	.	.	1	1	0.7	.	.	.
UROGENITAL SYSTEM	-ALL	1	1	0.7
	URINARY TRACT INFECTION	1	1	0.7

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

Reviewer comment: The rate of discontinuation due to AE among rasagiline-treated subjects in Cohort 1 (7.8 per 100 PY [1 mg]) was lower than that for Cohort 2 (11/100 PY [1 mg]). Although the subjects in Cohort 2 did have more advanced Parkinson's disease than those in Cohort 1, which may have contributed to the higher rate of discontinuations due to adverse events, to evaluate the low AE rate in Cohort 1 the disposition of discontinuing participants in TEMPO (the primary study in Cohort 1) were examined. The categories into which discontinuing subjects were divided are summarized in the table below.

FDA Table 27: Termination Reason for Subjects in the Cohort 1 Subject TEMPO (Adapted from TEMPO Study Report Table 7)

Termination Reason	Rasagiline 1 mg (N=134, 61 PYs)		Placebo (N=138, 63 PYs)	
	# Subjects	% Subjects	# Subjects	% Subjects
Adverse Event	5	3.7	1	0.7
Failed to Return	1	0.7	0	0
Subject Request	2	3	3	2.2
Unsatisfactory Response	0	0	1	0.7
Protocol Violation	0	0	0	0
Other	1	0.7	0	0

⁴⁰ The narrative for TEMPO #179 attributes the subject’s discontinuation to residual foot drop and ambulatory impairment following elective abdominal aortic aneurysm repair complicated by intraoperative myocardial infarction. The aneurysm had been diagnosed four years prior to study entry, and the surgery was performed approximately one year prior to study discontinuation.

Four rasagiline subjects were classified as discontinuing due to subject request: two within the rasagiline 1 mg/day treatment arm (shown in the table above), and two within the rasagiline 2 mg/day treatment arm. Case report forms within the NDA were not available for any of the four subjects. For one subject (#345), the TEMPO study report states that the subject and his wife wished to discontinue prematurely due to the subject's depression. This subject had been receiving rasagiline for approximately 17 months, and it was unclear why this discontinuation was classified as subject request instead of an adverse event, depression. Another subject (#424, on rasagiline 2 mg) also discontinued due to depression (as per Attachments 16.2 within the TEMPO study report), and was classified as "subject request" as well.

Additional information on the remaining two subjects discontinuing due to subject request was obtained from the sponsor through an e-mail request from the Safety Reviewer.⁴¹ Teva states that TEMPO #196 completed the placebo-controlled phase and chose not to continue in the active treatment phase because he had difficulty making study visits due to his work schedule. TEMPO #202 discontinued because she wanted to begin treatment with a medication disallowed by the study protocol. Teva also responded via e-mail that they had contacted the Parkinson's Study Group (PSG), which was responsible for much of the administration of the TEMPO trial, to ask why the two subjects experiencing depression had been classified as discontinuation due to subject request. The PSG representative suggested to Teva that this classification may have been made because the investigator considered the subject able to continue in the study in spite of the AE, but the subject chose not to do so.

As the number of subjects and AEs in Cohort 1 are relatively small, if the subjects who discontinued due to depression and who were classified as "subject request" were instead categorized as discontinuation due to adverse event, the rate of AEs in Cohort 1 would be similar to that of Cohort 2.

Among the other discontinuation categories, most of the subjects who classified as "protocol violation" were stated to have started a disallowed medication. Subjects in TEMPO whose symptoms were not well controlled with rasagiline alone could be moved to the active-control phase of the study, during which additional dopamine agonists or levodopa were allowed as per investigator discretion. The subjects discontinuing due to "Unsatisfactory Response" generally advanced to the active-control phase of the trial.

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

The sponsor states that an approximately equal number of patients in the rasagiline (N=16, 4.2%, 11/100 PYs) and placebo (N=19, 4.9%, 13/100 PY) groups of Cohort 2 terminated prematurely (ISS 14.4). The nervous system had the highest number of AEs associated with discontinuation: 1.8% of subjects on rasagiline and 3.1% of subjects on placebo. The sponsor reports that most AEs were recorded for only one participant. Exceptions to this were: abdominal pain (rasagiline 1mg n=3; placebo n=0), postural hypotension (rasagiline 1 mg n=2; placebo n=0), hallucinations (rasagiline 1 n=2;

⁴¹ E-mail correspondence with Teva, received April 28, 2004

placebo n=1) and dyspnea (rasagiline 1 mg n=2; placebo n=1). The sponsor table listing all premature terminations in Cohort 2 (Sponsor ISS Table 95) is provided in the Attachments 9.5 of this review.

For the individual studies comprising Cohort 2, in PRESTO⁴² thirteen patients (7.9%) on rasagiline 0.5 mg, nine patients (6.0%) on rasagiline 1 mg and nine patients (5.0%) on placebo discontinued the study early due to AE. An additional two patients with unspecified AEs on 0.5 mg were not included in the tabulated data. Teva reports that the body system with the highest incidence of AEs associated with premature discontinuation was the nervous system. As with Cohort 1 and Cohort 2 in general, the sponsor notes that most AEs were reported only once (ISS 14.4)

For LARGO, the sponsor states that 7/231 subjects (3%) in the rasagiline treatment group, 16/227 subjects (7%) in the entacapone treatment group, and 11/229 subjects (5%) in the placebo treatment group had an AE listed as the reason for their premature discontinuation from the study (LARGO 12.2.1.4).⁴³

Cohort 9: All Participants with PD Exposed to Rasagiline

Teva states that 10.1% (138/1360) of all PD patients exposed to rasagiline (Cohort 9) reported premature discontinuation due to AE, of which 9.4% (N=128) were coded as “dose stopped” (ISS 120 Day Update 5.5.3).

Reviewer comment: *As described at the beginning of this section, for some of the subjects classified as discontinuing due to AE, Teva states that a specific event could not pinpointed. These subjects were identified through their coding as “discontinuation due to AE,” but may not have been additionally coded as “dose stopped.” It is unclear from the ISS and the study reports at what stage in the study protocol and on what sponsor document this coding was done. Additional information will be requested from the sponsor to clarify this coding process. This may include asking Teva to list all AEs reported by subject with the dates of the AEs and the date of discontinuation.*

Of the 138⁴⁴ Cohort 9 members who discontinued: 23 (17% of total subjects exposed to 0.5 mg)⁴⁵ were receiving rasagiline 0.5 mg/day, 95 (14% of total subjects exposed to 1.0 mg) were receiving 1 mg/day, 17 (15% of total subjects exposed to 2 mg) were receiving

⁴² Exposures for the three treatment groups in PRESTO were similar: (1) *Rasagiline 0.5 mg*: 164 subjects, 76.2 patient-years, median treatment 183 days (2) *Rasagiline 1.0 mg*: 149 subjects, 69.6 patient-years, median treatment 183 days (3) *Placebo*: 159 subjects, 73.8 patient-years, median treatment 183 days (PRESTO Study Report 10.1).

⁴³ Exposures for the three treatment groups in LARGO were similar with respect to person-years of exposure and mean duration of treatment.

⁴⁴ The 138 subjects here refers to the total discontinuations in Cohort 9. As noted in the text above, Teva did not include the ten subjects for whom no specific AE leading to discontinuation was identified in the table of discontinuations, resulting in a total of 128 subjects in the sponsor table summarizing discontinuations due to AE. (This table is included in Appendix 9.6 of this review.)

⁴⁵ The total number of subjects exposed to the various dose groups within Cohort 9 were taken from Sponsor Table 4, 120 Day Safety Update.

2 mg/day, and 3 (60% of the total subjects exposed to 10 mg) were receiving 10 mg/day. The systems most frequently associated with early discontinuation were the nervous system (3.9%), followed by the cardiovascular system (2.7%), body as a whole (2.6%) and the digestive system (2.1%). The most common AEs occurring in subjects discontinuing early were hallucinations (n=14 [1.0%]), hypertension (n=9 [0.7%]), nausea (n=9 [0.7%]), dizziness (n=8 [0.6%]), accidental injury (n=7 [0.5%]), and postural hypotension (n=7 [0.5%]). A table summarizing all discontinuations for Cohort 9 provided in Attachments 9.6 of this report.

In ISS Attachments 18.7.3.4, Teva provides a listing of AEs resulting in discontinuation, which I reviewed. I also reviewed the narratives (and as needed additional sponsor documentation including case report forms) for all rasagiline-treated participants in TEMPO, PRESTO and LARGO who discontinued due to AEs. I found no events suggestive of pancreatitis, renal failure or hepatic failure, although several subjects discontinued due to abnormal hepatic or renal-related laboratory results (discussed below). Two cases of rhabdomyolysis occurred in rasagiline-treated participants who discontinued (PRESTO #58 and #628). These are discussed in section 4.6.2 (Serious Adverse Events) of this review. No participants discontinued due to creatinine kinase elevations, although this was not a routinely monitored laboratory test. Summaries of participants discontinuing due to selected AEs are presented below. The AEs chosen for discussion include those more frequently associated with discontinuation or those with the potential for more serious outcomes.

Abnormal Liver Function Tests

Three participants⁴⁶ discontinued due to liver function test abnormalities, which developed between 408 and 1618 days on rasagiline treatment. These cases are discussed further in Section 4.6.5 (Laboratory Data) of this review.

Increased BUN/Creatinine

TEMPO Ext. subject #123 experienced elevated BUN, creatinine and calcium after 357 days of treatment with rasagiline 1 mg. Details of this case are provided in Section 4.6.5 (Laboratory Data) of this review.

Hallucinations

Combining the two placebo-controlled cohorts, six rasagiline-treated participants and one placebo-treated participant had hallucinations coded as an AE associated with their early discontinuation. In Cohort 9 (all PD participants exposed to rasagiline), 14 subjects terminated prematurely due to hallucinations (120 Day Update Table 47).

Rasagiline-treated patients from the three pivotal trials and their corresponding extensions who terminated early after experiencing hallucinations are summarized below:

1. **TEMPO #273:** A 71 year-old man developed severe visual and auditory hallucinations after four days on rasagiline (1 mg/day), after which he discontinued the study. There was no recorded history of hallucinations on his case report form.

⁴⁶ TEMPO Ext. (TVP-1012233) #31, LARGO Ext. (TVP-1012/123) #31 and LARGO Ext. #83

2. **TEMPO #321:** A 73 year-old woman developed hallucinations after 25 days on treatment (2 mg/day). Hallucinations were described as severe but were not further characterized. The subject had a history of vivid dreaming and depression but not of prior hallucination.
3. **TEMPO #414:** A 59 year-old woman experienced sensory hallucinations (“worms under skin”) after approximately 10 days on treatment (2 mg/day). Symptoms were reported to have resolved two days after discontinuing rasagiline. The subject did not report a history of prior hallucinations.
4. **TEMPO Ext. #337:** This 71 year-old man discontinued rasagiline 2 mg/day after 272 days due to hallucinations (nature and severity not specified).
5. **PRESTO #119:** A 71-year-old woman experienced dyskinesia and hallucinations three days after beginning rasagiline (1 mg/day). After one week, she developed nausea and paresthesias, after which she discontinued the study. Hallucinations were reported to resolve approximately two months after discontinuation. The patient was receiving pergolide concomitantly
6. **PRESTO #145:** This 72 year-old man with a history of hallucinations discontinued rasagiline (0.5 mg/day) due to worsening hallucinations 23 days following randomization. The patient was receiving amantadine and ropinirole concomitantly.
7. **PRESTO #242:** A 78 year-old man with a history of vivid dreams who discontinued the study due to increased hallucinations developing 109 days following randomization to rasagiline 0.5 mg/day. The patient was receiving pramipexole, entacapone and pergolide concomitantly.
8. **PRESTO Ext.⁴⁷ #42:** This 73 year-old woman developed pneumonia approximately two months after beginning treatment with rasagiline (1 mg). She was hospitalized shortly thereafter for seizures, atrial fibrillation and hallucinations. She was found to be hyponatremic and treated for syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Most of her symptoms were reported to resolve, but she experienced increased depression, dysphagia and continuing pneumonia, and subsequently discontinued from the study. Concomitant medication before hospitalization included pramipexole, tamoxifen, pravastatin, gabapentin, and codeine.
9. **PRESTO Ext. #45:** An 80 year-old man with no reported psychiatric history developed severe hallucinations after 331 days receiving rasagiline 0.5 mg. The hallucinations were treated with quetiapine and risperidone, but persisted, and rasagiline was discontinued. The hallucinations were reported to continue, although well controlled by medication, after terminating the study.
10. **PRESTO Ext. #424:** This 47 year-old woman terminated early from the study after developing hallucinations following 216 days of rasagiline 1 mg/day.
11. **PRESTO Ext. #533:** This 64 year-old man experienced visual hallucinations on study drug day 189 (rasagiline 0.5 mg/day), and discontinued the study.
12. **TVP-1012/231⁴⁸ #105:** A 51 year-old man with a history of depression withdrew from the study after ten days of treatment with rasagiline 1 mg due to hallucinations.

⁴⁷ TVP-1012/135

⁴⁸ Study TVP-1012/231 was a placebo-controlled study of rasagiline monotherapy, and data from this study was pooled with the study TEMPO in Cohort 1.

13. **LARGO #60706:** A 71 year-old man experienced visual hallucinations while hospitalized with bacterial meningitis with multiple complications. He discontinued after 50 days on rasagiline 1 mg/day.
14. **LARGO Ext. #21806:** This 52 year-old man discontinued rasagiline treatment [the dosage in the LARGO Ext. study report narrative had not yet been unblinded] after 13 days due to agitation and hallucinations. The investigator attributed these to concomitant prednisolone initiated four days earlier for treatment of joint pain.

Reviewer comment: Studies of Parkinson's disease patients have estimated that between eight and forty percent will experience visual hallucinations during the course of their illness.⁴⁹ Hallucinations are also among the known side effects of several Parkinson's disease therapies, including levodopa and the MAO-B inhibitor selegiline. In the labeling for selegiline, hallucinations were listed as the second most frequent adverse event leading to discontinuation (after nausea) and was the fourth most frequently reported treatment emergent adverse event in a small placebo-controlled trial.

For general AEs in Cohort 1 (rasagiline monotherapy), three rasagiline-treated subjects (1 mg/day) experienced hallucinations (1.3%), versus two in the placebo-treated subjects (0.7%). In Cohort 2 (rasagiline as levodopa adjunct), hallucinations were slightly more frequent in the rasagiline-treated group (n=11, 2.9%) than in the placebo group (n=8, 2.1%) (ISS Table 38).

I reviewed the verbatim terms for all subjects in Cohort 9 who reported hallucinations, and found that only in the minority of cases was the nature of the hallucination (visual, auditory, etc.) specified. I also reviewed the case narratives for subjects who experienced psychosis. The sponsor notes that of the six rasagiline-treated subjects who reported psychosis as an adverse event, three had a previous history of delusions, hallucinations or paranoia, and four had a previous history of anxiety or depression (120 Day Safety Update 5.4.2). The narratives did not mention hallucinations as a prominent symptom in the psychotic episodes.

Blood Pressure Fluctuations⁵⁰ and Hypotension

In the placebo-controlled cohorts, three rasagiline-treated subjects discontinued due to blood pressure fluctuations (n=1) and postural hypotension (n=2), compared with none in the placebo group. For Cohort 9 members who discontinued prematurely due to AE, two were due to blood pressure fluctuations, two were due to hypotension, and seven were due to postural hypotension (120 Day Update Post-Text Table 47). Summaries of rasagiline-treated subjects who discontinued due to blood pressure fluctuations, including

⁴⁹ Barnes J, David JS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. *J Neurol Neurosurg Psychiatry* 2001;70 (June):727-33.

⁵⁰ The following subjects from clinical pharmacology (Phase I/II) studies also experienced blood pressure fluctuations and/or orthostatic hypotension: TVP-1012/111 #801, TVP-1012/111 #803, TVP-1012/111 #58, TVP-1012/111 #64, and TVP-1012/111 #113. These are addressed in the Clinical Pharmacology section of the review.

orthostatic hypotension are provided below.⁵¹ Hypertension, particularly in the context of potential tyramine interaction, is addressed in more detail in the Discussion section of this review.

1. **LARGO #60203:** A 68 year-old woman was withdrawn (after 51 days on treatment [1mg]) from the study due to blood pressure fluctuations: screening visit 120/74 and 140/80, baseline visit 100/65 and 120/80, Week 3 visit 105/60 (supine) and 120/70 (standing), Week 6 visit 140/80 and 170/90, termination visit 130/85 and 175/90. The patient had a history of hypertension and entered the study on concomitant hydrochlorothiazide, ramipril and doxazosin. Teva states that these blood pressure fluctuations continued after the subject terminated the study.
2. **LARGO # 16203:** This 71 year-old terminated the study after 77 days on treatment after experiencing blood pressure fluctuations, as summarized in the sponsor table below. The subject's narrative made no mention of a prior history of blood pressure fluctuations or anti-hypertensive treatment.

Visit	Date	SBP supine	SBP standing	DBP supine	DBP standing	SBP supine- standing	DBP supine- standing
Screening	01Nov2001	130	120	70	80	10	-10
Baseline	27Nov2001	130	130	90	90	0	0
Week 3	18Dec2001	110	110	80	80	0	0
Week 6	16Jan2002	120	120	80	80	0	0
Week 10	06Feb2002	100	100	70	70	0	0
Unscheduled	11Feb2002	140	70	100	?	70	?
Termination	25Feb2002	150	130	90	80	20	10

3. **PRESTO # 302:** A 63 year-old woman experienced dizziness and postural hypotension after approximately 60 days of treatment with rasagiline 1 mg, and chose to discontinue both rasagiline and the study at that time. She was diagnosed with a urinary tract infection one week later.
4. **PRESTO #532:** A 68 year-old man was hospitalized with intermittent dizziness and bilateral leg pain. Orthostatic hypotension was observed and rasagiline (1 mg/day) was discontinued 153 days following randomization. The patient was receiving pramipexole and entacapone concomitantly.
5. **PRESTO Ext. #343:** A 62 year-old woman experienced the blood pressure fluctuations shown below and discontinued after 221 days on rasagiline 1 mg.

Visit	Date	Supine BP	Standing BP
Baseline	17Jun2002	107/62	111/69
Unscheduled	10Jul2002	160/92	150/90
V1/Month1	18Jul2002	146/94	152/96
Termination	26Jul2002	146/82	140/84

6. **PRESTO Ext. #424:** A 47 year-old woman discontinued after 191 days of rasagiline 1 mg when she noted fatigue and dizziness with standing.
7. **PRESTO Ext. #603:** A 64 year-old man who discontinued rasagiline 1 mg after 344 days due to dizziness associated with changes in position. These symptoms resolved when rasagiline was temporarily discontinued, but returned when the drug was re-started.

Anemia

1. **LARGO #60706:** A 71 year-old man with multiple medical problems (described further in the *Hallucinations* section above), experienced anemia secondary to a pre-pyloric bleeding angioma 50 days after the initiation of treatment. He subsequently withdrew from the study.
2. **PRESTO #242:** A 78 year-old man (also described further in the *Hallucinations* section above) was reported to have been treated for anemia, type not specified, prior to his discontinuation.
3. **TEMPO Ext. #234:** A 41 year-old man developed anemia after 910 days on rasagiline 1 mg. He later experienced a severe hemorrhage secondary to a stomach ulcer.

Dermatologic

1. **TEMPO Ext. #52:** A 59 year-old male discontinued rasagiline 1 mg after 1376 days due to pruritus.
2. **LARGO #16408:** A 60 year-old man discontinued after 51 days on rasagiline 1 mg due to lower limb cellulitis, followed by bilateral lower limb edema and erythema noted one month later.
3. **LARGO Ext. #60905:** A 73 year-old man discontinued after 74 days of rasagiline 1 mg due to a pruritic rash on his thorax.
4. **PRESTO #206:** A 66 year-old woman discontinued rasagiline (0.5 mg/day) for one month (beginning study day 22) due to rash. She later permanently discontinued on study day 62 with continued rash (characterized as "raised, waist to toe"), diarrhea and dry skin. The patient was receiving concomitant ropinirole.
5. **PRESTO #620:** A 63-year-old man discontinued rasagiline (0.5 mg/day) on study day 10 due to generalized rash and urticaria starting nine days after randomization. Concomitant medications included pergolide.
6. **PRESTO #740:** A 62-year-old man experienced fever and diffuse confluent erythema of the face. As per the AE narrative in the PRESTO study report, the subject entered the study with normal hematology lab results. Treatment with antibiotics and steroids was initiated. Two days later, during his week 10 visit, the subject's absolute neutrophil count was above the clinically significant range (14.1 x

10^3 /uL) and his total WBC count was also above normal range.⁵² Rasagiline was stopped after 75 days on treatment, and the subject was diagnosed with leukocytoclastic vasculitis (by biopsy) after study discontinuation. The subject's erythema and fever were reported to have resolved and his neutrophils count returned to normal range.

***Reviewer Comment:** During my review of the above cases I found no evidence of mucocutaneous involvement or other symptoms associated with Stevens-Johnson syndrome. The dermatologic reactions appeared to be of a generally mild to moderate nature. In addition, the heterogeneity of the dermatological adverse events described above is less consistent with an association with rasagiline treatment. The occurrence of skin melanomas is discussed separately in Section 5.0 of this review.*

Vasculitis

Subject PRESTO #740 developed a leukocytoclastic vasculitis, as described above. Upon review of vascular AEs, other reports of vasculitis were not prominent (summarized in Section 6.10 [Vascular ROS] of this review). No cases of vasculitis were reported among the SAEs, although four serious reports were coded to the preferred term "vascular disorder." None of the verbatim terms for the COSTART term vascular disorder referred to a vasculitis, but instead described vascular stenosis, occlusions or aneurysms (Sponsor datafile AE-C9). The only subject who discontinued due to vasculitis was PRESTO #740, which was coded to the COSTART term skin vasculitis (120 Day Safety Update Post-Text Table 47, AE-C9).

Gastrointestinal

1. **TEMPO #130:** A 72 year-old woman initially randomized to placebo, later switched to rasagiline 2 mg/day in the active control phase. Several days prior to her first dose of rasagiline the subject reported dizziness. Shortly after taking her first dose of rasagiline she vomited, and stated she had vomited the undigested pill. She was treated at an Emergency room with intravenous fluids for persistent nausea and dizziness, after which she improved and was discharged home. She declined to re-start rasagiline.
2. **LARGO #61409:** A 62 year-old woman terminated after 106 days of rasagiline (1 mg/day) due to gastric pain.
3. **PRESTO #59:** A 72 year-old man discontinued the study due to increased drowsiness⁵³ and gastrointestinal distress after 12 days on treatment. The patient was receiving pramipexole concomitantly.
4. **PRESTO #447:** This 69 year-old woman discontinued due to abdominal "pressure," nausea and headache after three days of treatment with rasagiline 1 mg.
5. **PRESTO #493:** A 78 year-old woman discontinued prematurely after 31 days of rasagiline treatment (0.5 mg/day) due to persistent nausea and increased dyskinesia. She was receiving pramipexole concomitantly.

⁵² The exact value of the WBC count was not provided by the sponsor.

⁵³ Sleep disorders as an adverse event associated with rasagiline are discussed in more detail in Section 4.6.4 (Common Adverse Events) of this review.

6. **PRESTO #557:** A 57-year-old woman experienced diarrhea, nausea and abdominal pain two weeks after randomization. The subject temporarily discontinued rasagiline (0.5 mg/day) on study day 24, with improvement of all symptoms. However, after the subject restarted the study drug the diarrhea reoccurred, and the study drug was stopped 69 days following randomization. The patient was receiving entacapone concomitantly.
7. **LARGO Ext. #15610:** Summarized in the *Hallucinations* section above – also experienced a gastrointestinal disorder of unknown etiology.
8. **LARGO Ext. #41702:** A 52 year-old man who discontinued rasagiline 1 mg after developing nausea, vomiting and dizziness approximately 131 days after randomization.
9. **LARGO Ext. # 60709:** This 61 year-old woman developed severe dyspepsia and nausea after 25 days of rasagiline treatment (1 mg), and subsequently discontinued.
10. **LARGO Ext. #61403:** This 69 year-old woman experienced abdominal pain, was later diagnosed with an intestinal perforation, and discontinued rasagiline on treatment day 112.
11. **PRESTO Ext. #59:** A 72 year-old man who discontinued due to dyspepsia and somnolence, with onset between nine and eleven days after beginning rasagiline 1 mg.

4.6.4 Common Adverse Events

Common AEs from Re-Coded AE Dictionary

As discussed in Section 4.4 of this review, the FDA requested that Teva make the following revisions in the AE dictionary initially submitted with the NDA:

- All falls be coded to both a new preferred term (PT) “FALLS”, and a reasonable PT for the precipitant or resultant verbatim term⁵⁴;
- Colds/upper respiratory (URI) infections be removed from “INFECTIONS” to a new PT “COLD;” and
- Several cases of “stomach-flu” be re-classified under the PT “GASTROENTERITIS.”

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

Teva states that 82.6 % of subjects receiving rasagiline monotherapy (1 mg) and 80.1% of participants receiving placebo reported AEs of any kind, over half of which were first noted in the initial four weeks of treatment (Clinical Overview 2.5.5.2, ISS Table 31). Common and most common AEs for Cohort 1 members are summarized in the tables below. Teva defined “common” AEs as those with incidence of $\geq 2\%$ in the rasagiline 1 mg group and numerically greater than in the placebo group, or similarly for “most common” AEs but with an incidence at least twice that of placebo (ISS 6.2.1.1).

⁵⁴ For example, fall with hip fracture would be coded to “FALL” and “ACCIDENTAL INJURY.”

Reviewer comment: The sponsor's criteria for most common AEs seems to address drug relatedness more than commonality.

FDA Table 28: Most Common AEs for Cohort 1 (Adapted from Sponsor ISS Table 35 and Sponsor 120 Day Safety Update Table 52)

Most Common AEs in Cohort 1		Rasagiline 1 mg (N=149)		Placebo (N=151)		Relative Risk (Rasagiline to Placebo)
		No. of Patients	% of Patients	No. of Patients	% of Patients	
Body as a Whole	Flu Syndrome	7	4.7	1	0.7	8.6
	Infection*	3	2.0	1	0.7	2.9
	Fever	4	2.7	2	1.3	2.1
	Malaise	3	2.0	--	--	--
	Neck Pain	3	2.0	--	--	--
	Neoplasm	3	2.0	--	--	--
Musculoskeletal System	Arthritis	3	2.0	1	0.7	2.9
Nervous System	Depression	8	5.4	3	2.0	2.7
	Vertigo	3	2.0	1	0.7	2.9
Respiratory System	Rhinitis	4	2.7	3	1.3	2.1
Special Senses	Conjunctivitis	4	2.7	1	0.7	3.9
Digestive System	Gastroenteritis*	4	2.7	2	1.3	2.1
Hemic System	Ecchymosis*	3	2.0	--	--	--

* As a result of verbatim to preferred term (PT) re-coding (discussed below), infection, gastroenteritis and ecchymosis should also be included among the most common AEs for Cohort 1.

FDA Table 29: Common AEs by Body System and COSTART Term in Cohort 1 (Sponsor ISS Table 34)*

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		Rasagiline 1 mg (N=149)		Placebo (N=151)	
		No. of Patients	% of Patients	No. of Patients	% of Patients
BODY AS A WHOLE	HEADACHE	21	14.1	18	11.9
	FLU SYNDROME	9	6.0	1	0.7
	CHEST PAIN	6	4.0	6	4.0
	FEVER	4	2.7	2	1.3
	MALAISE	3	2.0	.	.
	NECK PAIN	3	2.0	.	.
	NEOPLASM	3	2.0	.	.
DIGESTIVE SYSTEM	DYSPEPSIA	10	6.7	6	4.0
	DIARRHEA	9	6.0	9	6.0
MUSCULOSKELETAL SYSTEM	ARTHRALGIA	11	7.4	6	4.0
	ARTHRITIS	3	2.0	1	0.7
NERVOUS SYSTEM	DIZZINESS	17	11.4	16	10.6
	DEPRESSION	8	5.4	3	2.0
	SLEEP DISORDER	6	4.0	6	4.0
	PARESTHESIA	3	2.0	2	1.3
	VERTIGO	3	2.0	1	0.7
RESPIRATORY SYSTEM	SINUSITIS	6	4.0	6	4.0
	PHARYNGITIS	4	2.7	4	2.6
	RHINITIS	4	2.7	2	1.3
SPECIAL SENSES	CONJUNCTIVITIS	4	2.7	1	0.7

*As a result of verbatim to preferred term (PT) re-coding (discussed below), falls should also be included among the common AEs for Cohort 1 (rasagiline 4.7%, n=7; placebo 2.6%, n=4)

Dose-response data (comparing rasagiline 1 and 2 mg within the TEMPO study) was available for Cohort 1 (ISS 6.2.1.1). The sponsor notes that reports of arthralgia⁵⁵ were more frequent in the 2 mg treatment group (10.3%) than 1 mg (7.4%) or placebo (4.0%) group, which may indicate a dose response. The sponsor asserts that the other AEs classified as common in the rasagiline 1 mg group did not demonstrate a dose-response relationship (ISS Table 35).⁵⁶

The sponsor states that when the common AEs of the rasagiline 2 mg group are listed in descending order of difference over placebo, a trend towards increased AEs of the nervous system and gastrointestinal system is observed in comparison to the 1 mg treatment group (ISS 6.2.1.1). Teva notes that AEs that meet criteria for common AEs for the rasagiline 2 mg, but not 1 mg, group were: abnormal dreams (3.4% 2 mg, 0.7% 1 mg, 0% placebo), sleep disorder, somnolence, ataxia (mainly imbalance), flatulence, and vomiting (2.7% 2 mg, 1.3% 1 mg, 0.7% placebo)⁵⁷ (ISS Table 37). The sponsor theorizes that increased dopaminergic effects of rasagiline 2 mg (versus 1 mg) could explain some

⁵⁵ Teva states that in Cohorts 1 and 2 “arthralgia” consisted of pain in a single joint for most participants reporting this AE, rather than a polyarticular syndrome.

⁵⁶ The common AEs examined by the sponsor (and reviewed by myself) and not demonstrating a clear dose response (Sponsor Table 36) were flu syndrome, depression, dyspepsia, headache, conjunctivitis, malaise, neck pain, and neoplasm.

⁵⁷ I reviewed the corresponding sponsor table, and the common AEs for which I included percentages were those displaying a possible dose response relationship.

of these differences. Teva notes that reports of somnolence, a possible dopaminergic agent effect, were less frequent in the rasagiline 1 mg group (0.7%) than the placebo group (1.3%), although they were more frequent in the rasagiline 2 mg group (3.4%). Sleep disorders are discussed in more detail later in this section of the review.

Teva noted that following re-coding, in Cohort 1 the new PT “Falls” meets criteria for common AEs. In addition, ecchymosis, gastroenteritis, and infection would meet criteria for “most common” AEs in Cohort 1 (120 Day Safety Update 7.3.2.1).

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

The sponsor states that compared to Cohort 1, the common AEs of Cohort 2 members occurred more frequently in the cardiovascular, digestive and nervous systems, and less often in the body as a whole and respiratory system (ISS 6.2.1.2). Teva asserts that concomitant levodopa treatment could be expected to increase dopaminergic AEs in this cohort. Arthralgia is seen to a lesser extent in this cohort (7.4% rasagiline 1 mg in Cohort 1 versus 3.2 % rasagiline 1 mg in Cohort 2)(Section 6.2.1.2). Teva noted that abdominal pain was often seen in association with other symptoms, such as nausea, constipation and diarrhea, and was classified as serious in two cases (discussed in Section 4.6.2 [Serious Adverse Events] of this review).

Reviewer comment: *The occurrence of an excess of arthralgia and flu syndrome in rasagiline-treated subjects in Cohort 2 is addressed in more detail in Section 4.6.4.3 below.*

In Cohort 2, as a result of re-coding of falls, ecchymosis and the new PTs FALLS and COLD were classified as common AEs. Accidental injury was reclassified from common to most common and arthralgia from most common to common AE (120 Day Safety Update 7.3.2.2).

FDA Table 30: Most Common AEs in Cohort 2 (Sponsor ISS Table 39)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)		Placebo (N=388)	
		No. of Patients	% of Patients	No. of Patients	% of Patients
BODY AS A WHOLE	ABDOMINAL PAIN	15	3.9	5	1.3
CARDIOVASCULAR SYSTEM	POSTURAL HYPOTENSION	18	4.7	5	1.3
DIGESTIVE SYSTEM	CONSTIPATION	16	4.2	8	2.1
	VOMITING	13	3.4	4	1.0
	ANOREXIA	8	2.1	2	0.5
METABOLIC AND NUTRITIONAL DISORDERS	WEIGHT LOSS	16	4.2	6	1.5
MUSCULOSKELETAL SYSTEM	ARTHRALGIA	12	3.2	5	1.3
NERVOUS SYSTEM	DYSTONIA	9	2.4	3	0.8
	ABNORMAL DREAMS	8	2.1	3	0.8

FDA Table 31: Common AEs in Cohort 2 (Adapted from Sponsor ISS Table 40)

Rasagiline ISS Cohort 2: Placebo-Controlled Studies Levodopa-Treated Fluctuating Patients	Rasagiline 1 mg (N=380)		Placebo (N=388)		Relative Risk: Rasagiline to Placebo
	No. of Patients	% of Patients	No. of Patients	% of Patients	
DYSKINESIA	39	10.3	25	6.4	1.6
POSTURAL HYPOTENSION	18	4.7	5	1.3	3.6
ACCIDENTAL INJURY	31	8.2	20	5.2	1.6
WEIGHT LOSS	16	4.2	6	1.5	2.7
ABDOMINAL PAIN	15	3.9	5	1.3	3.0
VOMITING	13	3.4	4	1.0	3.3
CONSTIPATION	16	4.2	8	2.1	2.0

The data from PRESTO, which included two rasagiline dose groups (0.5 mg and 1 mg) allows for dose-response assessment. The sponsor states that AEs occurring in at least 2% of the 0.5 mg treated subjects, which are at least 2% increased over placebo and which show a possible dose-response in relation to the 1 mg group were: accidental injury (17.4% 1 mg, 14.6% 0.5 mg, 10.1% placebo), arthralgia (8.1% 1 mg, 5.5% 0.5 mg, 2.5% placebo), postural hypotension (8.7% 1.0 mg, 6.1% 0.5 mg, 3.1% placebo) and vomiting (6.7% 1 mg, 3.7% 0.5 mg, 1.3% placebo) (ISS Table 41).

Common AEs in the rasagiline-treated participants in LARGO were generally similar to those of Cohort 2 overall, with the exception of three participants experiencing first degree AV block (see table below.)

FDA Table 32: LARGO AEs with a 1.0% or Greater Difference Between the Rasagiline and Placebo Treatment Group (Sponsor Table 41, LARGO Study Report)

Table 41. Adverse Experiences with at least a +1.0% difference between the Rasagiline and Placebo Treatment Groups by decreasing order of the difference in incidence

TVP-1012/122 (LARGO)	Rasagiline 1 mg (N=231)		Placebo (N=229)		Difference
	N	%	N	%	
POSTURAL HYPOTENSION	5.0	2.2	.	.	2.2
ABDOMINAL PAIN	7.0	3.0	3.0	1.3	1.7
DYSTONIA	5.0	2.2	1.0	0.4	1.7
AV BLOCK FIRST DEGREE	3.0	1.3	.	.	1.3
CONSTIPATION	3.0	1.3	.	.	1.3
DYSKINESIA	12.0	5.2	9.0	3.9	1.3
PAIN	4.0	1.7	1.0	0.4	1.3

Cohort 3: Rasagiline without Levodopa - Any Treatment Duration

The sponsor states that when the rates of AEs are ranked, the most frequent AEs were: infection (21.8/100 PYs), headache (20.9/100 PYs), accidental injury (17.5/100 PYs), pain (11.4/100 PYs), dizziness (11.4/100 PYs), arthralgia (10.6/100 PYs), back pain (10.0/100 PYs), nausea (8.6/100 PYs), postural hypotension (7.3/100 PYs), myalgia (7.0/100 PYs), sleep disorder (6.9 reports), constipation (6.5/100 PYs), depression (6.4/100 PYs), and dyspepsia (6.0/100 PYs) (ISS 6.2.2.1).

The sponsor notes that for common AEs (≥ 10 reports/100 PYs)⁵⁸ in Cohort 3, five (infection, headache, accidental injury, pain, and dizziness) are also seen for all treatment groups in Cohort 1. The sponsor therefore suggests these AEs may be typical of the older population typically associated with PD patients, and unrelated to the drug.

Reviewer Comment: For the five AEs discussed immediately above, rates for the placebo group of Cohort 1 were somewhat higher than for the Cohort 3 rasagiline-treated group. It should be noted that patients on rasagiline for “any treatment duration” include those patients who tolerated rasagiline well enough to remain on it. Such patients contribute person-time to the denominator without adding AEs to the numerator. Thus it is not unexpected that the rates of specific AEs are lower in Cohort 3 as compared to placebo treated patients from Cohort 1.

Cohort 4: Rasagiline without Levodopa - Long Term (>1 year) Treatment

The sponsor states that AE rates for Cohort 4 (long-term treatment) are stable or decreased compared to Cohort 3 (any treatment duration). Teva therefore asserts that no long term cumulative effect of rasagiline is demonstrated by this cohort (ISS 6.2.2.2).

FDA Table 33: Rate and Percent of Common AEs in Cohort 4 Compared to Cohort 3 (Adapted from Sponsor Post-Text Table 70 and 71)

Rasagiline ISS Cohort 3 & 4 (Rasagiline monotherapy)	Cohort 3 – Any Treatment Rasagiline (N=377, PYs=752.2)				Cohort 4 – Long Term Rasagiline (N=252, PYs 690.6)			
	No. of Repts	No. of Pts.	% of Pts.	Repts. Per 100 PYs	No. of Repts.	No. of Pts.	% of Pts.	Repts. Per 100 PYs
INFECTION	164	102	27	22.3	149	21.6	88	34.9
HEADACHE	157	65	17	21.2	128	18.5	47	18.7
ACCIDENTAL INJURY	132	77	20	18.8	107	15.5	61	24.2
PAIN	86	38	10	11.4	76	11.0	29	11.5
DIZZINESS	86	54	14	11.4	75	10.9	45	17.9
ARTHRALGIA	80	54	14	10.6	73	10.6	48	19.0

⁵⁸ In the rasagiline-treated cohorts without placebo control, common AEs were defined as AEs with at least ten reports per 100 patient years. The appropriateness of this criterion for common AEs is examined in Section 4.3 of this review.

Reviewer Comment: As noted previously, patients remaining on rasagiline long-term are likely contributing person time without associated adverse events, so one could expect the rate of common AEs in Cohort 4 (Long-Term Treatment) to be lower than that for Cohort 3 (Any Treatment Duration). However, for the common AEs summarized in the table above this is generally not the case.

Cohort 5: Rasagiline as Levodopa Adjunct in Non-Fluctuating Patients - Any Treatment Duration

A table of the most common AEs in Cohort 5 is presented in comparison with the corresponding Cohort 6 AE data in the Cohort 6 section below. The sponsor states that when compared to Cohort 3 (rasagiline monotherapy - any treatment duration), accidental injury, arthralgia, nausea, postural hypotension, somnolence and sleep disorders were reported more frequently in Cohort 5, which Teva asserts would be consistent with the addition of concomitant levodopa treatment (ISS 6.2.2.3).

Reviewer Comment: Cohort 5 was composed of 154 participants from TEMPO (the active treatment phase) and/or its open label extension for whom levodopa therapy was added to rasagiline monotherapy. The sponsor notes that some of the patients in this cohort may have become fluctuators as their disease progressed.

For the cardiovascular system, the sponsor notes that compared to Cohort 3 there was more syncope (4.2/100 PYs Cohort 5 versus 1.2/100 PYs Cohort 3) and ECGs classified as abnormal (3.0/100 PYs Cohort 5 versus 1.2/100 PYs Cohort 3), and less atrial fibrillation (0.4/100PYs Cohort 5 versus 1.9/100 PYs Cohort 3). When AEs related to myocardial ischemic events were combined (e.g., angina, myocardial ischemia and infarction, coronary artery disorder, coronary occlusion), similar rates were seen between Cohort 5 (3.3 reports/100 PYs), Cohort 3 (3.9 reports/100 PYs) and Cohort 4 (3.5 reports/100 PYs). Teva reports that nervous system AEs in general (84.7/100 PYs) and dyskinesia (3.4/100 PYs) in particular were increased in Cohort 5 (in which levodopa was added to the treatment of initially monotherapy patients), compared to the strictly rasagiline monotherapy Cohorts 3 and 4. The sponsor asserts that many of the frequently reported AEs in this cohort reflect the dopaminergic effects associated with levodopa (ISS 6.2.2.3).

Teva states that higher rates of skin carcinoma (5.5 repts./100 PYs in Cohort 5 versus 3.3/100 PYs in Cohort 3) and benign skin neoplasm (4.0 reports/100 PYs in Cohort 5 versus 0.9/100 PYs in Cohort 3) were observed for this cohort⁵⁹ (ISS 6.2.2.3). However, Teva notes that two patients with multiple lesions accounted for more than half of the 43 reports of basal cell and squamous cell carcinomas in this cohort: TVP-1012/233 #173 with 14 reports and TVP-1012/233 #269 with 10 reports. The sponsor asserts that possible overdiagnosis of some lesions lacking pathological confirmation, duplicate coding of both the initial diagnosis and the definitive excision of lesions, and especially the introduction of proactive dermatological surveillance contributed to an enhanced

⁵⁹ As per the lack of overlap between subjects coded to the preferred term skin carcinoma and the preferred term melanoma, the sponsor treated melanoma and skin carcinoma as separate categories of adverse events. Melanomas were therefore not subsumed within the skin carcinoma category.

diagnosis of malignant and benign skin lesions within this cohort (120 Day Update 5.3.1).⁶⁰

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

The sponsor states that compared to Cohort 5, this long term cohort had a slight increase in the rate of skin carcinoma, arthralgia and back pain, and a slight decrease in nausea, postural hypotension and somnolence (See table below) (120 Day Update 5.3.2).

FDA Table 34: Rate and Percent of the Ten Most Common AES in Cohort 5 and 6 (Adapted from Sponsor Table 25 and 24, 120 Day Safety Update)

Rasagiline ISS Cohort 5 & 6: LD-Treated Non- Fluctuating Patients	Cohort 5: Any Treatment Rasagiline (N=183, 335.2 PYs)				Cohort 6: Long Term Rasagiline (N=108, 304.2 PYs)			
	No. of Repts	No. of Pts.	% of Pts.	Repts. Per 100 PYs	No. of Repts	No. of Pts.	% of Pts.	Repts. Per 100 PYs
ACCIDENTAL INJURY	80	40	21.9	23.9	69	33	30.6	22.7
INFECTION	49	37	20.2	14.6	43	31	28.7	14.1
SKIN CARCINOMA	43	14	7.7	12.8	42	13	12.0	13.8
ARTHRALGIA	40	25	13.7	11.9	39	24	22.2	12.8
NAUSEA	43	37	20.2	12.8	34	28	25.9	11.2
PAIN	35	29	15.8	10.4	32	26	24.1	10.5
BACK PAIN	25	21	11.5	7.5	25	21	19.4	8.2
POSTURAL HYPOTENSION	33	22	12.0	9.8	24	16	14.8	7.9
CONSTIPATION	27	15	8.2	8.1	24	19	17.6	7.9
SOMNOLENCE	34	30	10.1	10.1	24	22	20.4	7.9

Cohort 7: Rasagiline as Levodopa Adjunct in Fluctuating Patients – Any Treatment Duration

The sponsor states that overall the most frequently reported AEs in this cohort were fairly similar to those of the rasagiline or placebo treatment groups of Cohort 2 (short-term levodopa adjunctive therapy). AEs meeting criterion for most common in Cohort 2, but not in Cohort 7, included abdominal pain, vomiting, constipation and weight loss (120 Day Safety Update 5.3.3). The following AEs met the criteria for common AEs in Cohort 7, but not in Cohort 2: infection (6.1% rasagiline, 6.2% placebo in Cohort 2), urinary tract infection (4.7% rasagiline, 4.9% placebo in Cohort 2), and back pain (3.2% rasagiline, 3.9% placebo in Cohort 2).

⁶⁰ The occurrence of malignant melanoma within the rasagiline development program is discussed in more detail in Section 5.0 of this review.

FDA Table 35: Rate and Percent of the Ten Most Common AES in Cohort 7 and 8
(Adapted from Sponsor Table 26 and 27, 120 Day Safety Update)

Rasagiline ISS Cohort 7 & 8: LD-Treated Non- Fluctuating Patients	Cohort 7: Any Treatment Rasagiline (N=666, 582.7PYs)				Cohort 8: Long Term Rasagiline (N=249, 349.6 PYs)			
	No. of Repts	No. of Pts.	% of Pts.	Repts. Per 100 PYs	No. of Repts	No. of Pts.	% of Pts.	Repts. Per 100 PYs
DYSKINESA	119	91	13.7	20.4	43	31	12.3	12.4
ACCIDENTAL INJURY	108	71	18.5	10.7	42	27	12.0	10.8
DIZZINESS	70	44	12.0	6.6	21	15	6.0	6.0
NAUSEA	66	47	11.3	7.1	26	17	7.4	6.8
INFECTION	62	49	10.6	7.4	32	24	9.2	9.6
SLEEP DISORDER	61	57	10.5	8.6	61	57	8.6	10.5
URINARY TRACT INFECTION	48	37	8.2	5.6	48	37	5.6	8.2
BACK PAIN	47	33	8.1	5.0	28	21	8.0	8.4
POSTURAL HYPOTENSIO N	47	36	8.1	5.4	47	36	5.4	8.1
ARTHRALGIA	47	32	8.1	4.8	24	15	6.9	6.0

Cohort 8: Rasagiline as Levodopa Adjunct in Fluctuating Patients - Long Term Treatment

The sponsor states that AE rates in the long-term Cohort 8 (266 reports/100 PYs) decreased slightly compared to Cohort 7 (386 reports/100 PYs) (120 Day Safety Update 5.3.4)

Teva reports that the most frequently reported AEs in this cohort were dyskinesia, accidental injury, infection, back pain and nausea (see table above). In Cohort 2, headache and depression were seen more commonly in the placebo group; in comparison, among this long-term cohort of rasagiline-treated patients, the incidence decreased slightly for headache and increased slightly for depression. The sponsor reports that weight loss was one of the most common AEs in Cohort 2 (4.2% in rasagiline-treated subjects compared to 1.5% in placebo), and is slightly more common in the long-term Cohort 8 (6.4%) (120 Day Update 5.3.3.). Teva hypothesizes that weight loss, a possible dopaminergic effect, could become more prominent over time.

Reviewer comment: Regarding the timing of weight loss as an AE, the sponsor's statement of a possible increase with length of use appears to be based on analysis of the long-term cohort, rather than time to AE for individual subjects experiencing weight loss.

Cohort 9: All PD Patients Ever Exposed to Rasagiline

Teva reports that AEs of any kind were reported by 82.7% of Cohort 9 members (Clinical Overview 2.5.5.2). When ranked in descending order of the AE rates⁶¹ (see table below), the most commonly reported AEs included infection, accidental injury, dizziness, headache and pain, which were also among the most common AEs in the placebo groups of Cohort 1 and 2 (120 Day Update 5.3.5). The sponsor proposes that dyskinesia, nausea, sleep disorder and postural hypotension may be expected with dopaminergic therapy, and further notes that arthralgia was a common AE of the rasagiline-treated groups in the placebo-controlled studies (120 Day Update 5.3.5) Teva therefore concluded there were no unexpected findings for common AE within this inclusive cohort.

Reviewer comment: Although Teva notes that no unexpected findings were identified in this “all exposed” cohort, it should be stated that cohorts composed of all exposed subjects are best suited for identifying uncommon events, and less suited to identify common events.

FDA Table 36: Rate and Percent of the Ten Most Common AEs in Cohort 9 (Sponsor Table 28, 120 Day Safety Update)

120 Day Update of Rasagiline ISS Cohort No. 9: All Parkinson’s Disease Patients Ever Exposed to Rasagiline	Rasagiline (N=1360, Patient-Years=2017.2)			
	No. of Reports	No. of Reports Per 100 Patient Years	No. of Patients	% of Patients
ACCIDENTAL INJURY	425	21.1	239	17.6
INFECTION	367	18.2	241	17.7
HEADACHE	303	15.0	140	10.3
DIZZINESS	262	13.0	174	12.8
NAUSEA	232	11.5	168	12.4
ARTHRALGIA	226	11.2	146	10.7
PAIN	204	10.1	135	9.9
DYSKINESIA	203	10.1	145	10.7
SLEEP DISORDER	189	9.4	161	11.8
POSTURAL HYPOTENSION	171	8.5	106	7.8

*Ten most frequent AEs by time-adjusted frequency

The sponsor reports that 20.4% of frequently reported AEs were classified as severe, with the highest percentages reported for accidental injury (2.9%), back pain (1.1%) and dyskinesia and extrapyramidal syndrome (1.0% each) (120 Day Update 5.3.5)

⁶¹ The sponsor states that due to the wide variation of rasagiline exposure in this group, the number of reports standardized to exposure (in terms of 100 PYs) was selected as the most appropriate method to present AE occurrence.

4.6.4.1 Special Issues: Sleep Disorders

Sleep disorders have been associated with other Parkinson's disease therapies, most notably the dopamine agonists. In the rasagiline development program, sleep disorder⁶² was reported by 11.8% (n=161) of all Parkinson's disease patients exposed to rasagiline. An additional 109 subjects (from sponsor Cohort 9 dataset AE_C9) experienced somnolence. The sponsor appeared to have generally coded subject reports of "drowsiness" or "sleepiness" to somnolence, while subject descriptions of insomnia or difficulty sleeping were coded to the preferred term sleep disorder.

In the two placebo-controlled cohorts, the number and percentage of subjects reporting sleep disorders in the rasagiline treatment groups was somewhat higher than in the placebo group (For Cohort 1 - rasagiline 5.1%, n=15, placebo 4.0%, n=6); Cohort 2 - rasagiline 5.0%, n=19; placebo 4.1%, n=16.) Two other sleep-related AEs were moderately higher in rasagiline-treated subjects compared to placebo: somnolence (Cohort 1 - rasagiline 2.0%, n=6; placebo 1.3%, n=2; Cohort 2 - rasagiline 3.2%, n=12; placebo 2.3%, n=9), and abnormal dreams (Cohort 1 - rasagiline 2.0%, n=6; placebo n=0; Cohort 2 - rasagiline 2.1%, n=8; placebo 0.8%, n=3.) Somnolence was recorded among the AEs of premature termination for one patient on rasagiline 1 mg and one on placebo (ISS 6.9.1.6).

A particularly serious concern, and one observed with the use of dopamine agonists, are sleep disorders with sudden onset. I searched the AE verbatim terms within the sponsor dataset for Cohort 9 (file AE_C9) for the following key words: sleep, attack and/or sudden. This revealed three rasagiline-treated (1 mg/day) subjects, all participants in the TEMPO extension study, who experienced either "sleep attacks" (TVP-1012/233 #323) or "sudden sleepiness" (TVP-1012/233 #200, TVP-1012/233 #316). All three were receiving concomitant dopamine agonists, however.⁶³ Time to onset of these AEs was study drug day 216, 580 and 1394.

4.6.4.2 Special Issues: Orthostatic Hypotension⁶⁴

The topic of orthostatic hypotension is also discussed in Section 4.6.3 (Discontinuations) above. A total of 139 verbatim reports of postural hypotension were listed in the sponsor dataset "AE-9" (containing AEs for Cohort 9) within the Case Report Tabulations (CRT) section of the NDA. The mean time to report of orthostatic hypotension was 284 days, with a range from 2 to 1415 days. The distribution of the time to onset of orthostatic hypotension is further displayed in the table below. As per the graph, although 26% of subjects reporting orthostatic hypotension did so in the first two months, a strong

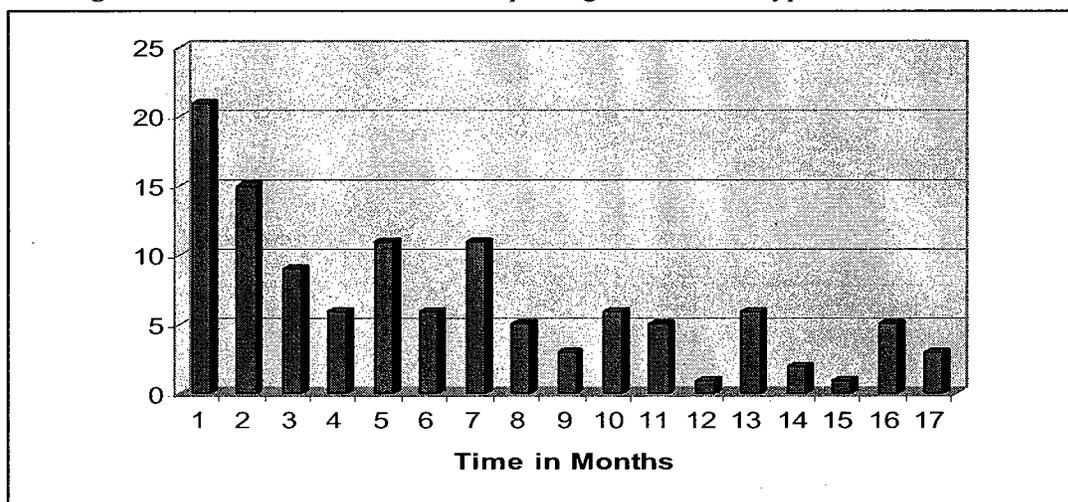
⁶² The following verbatim terms were coded to the preferred term sleep disorder: insomnia, difficulty sleeping, sleep disturbance, sleeplessness, and sleep problems. These terms are a convenience sample taken from sponsor data set "AE-C9," which included AE data for Cohort 9.

⁶³ E-mail communication from the sponsor received April 29, 2004.

⁶⁴ Verbatim terms categorized to the Preferred Term Postural Hypotension included the following: dizziness when he stands, light-headed when he stood up, lightheadness with position change, postural hypotension, orthostatic hypotension, and worsening of orthostasis.

temporal pattern does not appear to be present. However, when examining the figure below, it should be kept in mind that patients are dropping out over time. Thus the denominator for each subsequent month is smaller than the previous. As such, the proportion of patients reporting an AE of orthostatic hypotension is probably not dropping as much over time as it appears in the figure.

FDA Figure 1: Distribution of Time to Reporting Orthostatic Hypotension in Cohort 9⁶⁵



An additional 23 subjects (not included in the graph above due to space considerations) experienced postural hypotension following 18 to 47 months of rasagiline exposure.

A similar relationship is seen when Cohort 1 and Cohort 2 subjects are examined separately, with the largest number of cases per month occurring in the first two months of rasagiline exposure. However, a higher percentage of subjects in Cohort 2 (43%) who experienced postural hypotension did so in the first two months, compared to 14% of total cases in Cohort 1 occurring in the first two months of treatment.

4.6.4.3 Special Issues: Flu Syndrome and Arthralgia

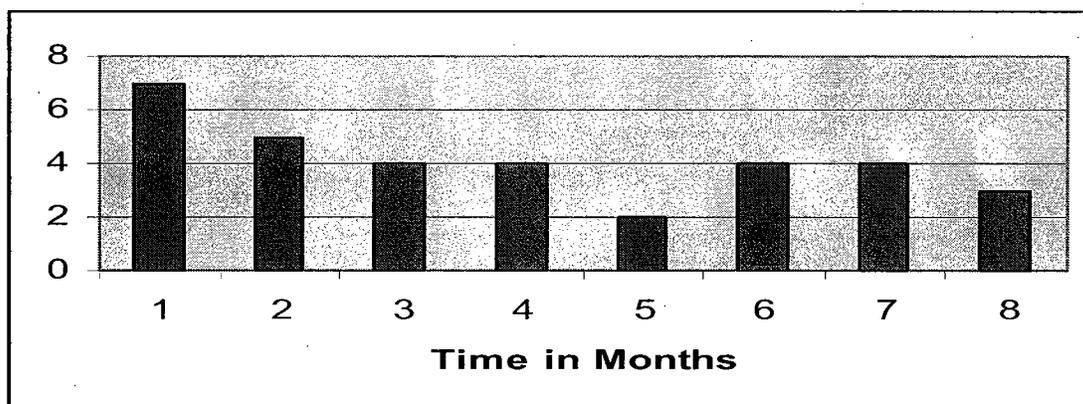
Although flu-like symptoms may be a relatively common adverse event in the general population, in Cohort 1 there is a substantial excess of reports of flu-like symptoms in rasagiline-treated subjects compared to placebo subjects. In Cohort 1, 4.7%⁶⁶ of rasagiline-treated subjects reported flu syndrome, compared to 0.7% in placebo-treated subjects: a 6.7-fold excess in the rasagiline treatment group. The sponsor did not provide additional analyses or commentary on this excess of cases.

⁶⁵ The X-axis of the graph represents time in months (one month=30 days), and the Y-axis gives the number of subjects within each month-long period.

⁶⁶ The 4.7% flu syndrome in rasagiline-treated subjects represents the percent following the FDA-requested revision of the coding of certain verbatim terms, and was submitted with the 120 Day Safety Update. In the initial NDA submission, 6.0% of rasagiline-treated Cohort 1 subjects were reported to have experienced flu syndrome, but a number of these were cases of gastroenteritis inappropriately classified as flu from the verbatim term “stomach flu.”

The time to report of flu syndrome ranged from one to 1475 days, with an average of 355 days and a median of 308 days. The distribution overtime is summarized in the table below.

FDA Figure 2: Distribution of Time to Reporting Flu Syndrome in Cohort 9*



*There were additional cases beyond month eight (not shown). The month eight bar contains only cases within month eight, and does not represent cases in month eight and beyond.

The verbatim terms for flu syndrome typically consisted solely of “flu” or “flu syndrome,” and generally did not elaborate on specific symptoms (Sponsor datafile AE_C9). Of the 70 preferred terms for flu, in only four cases did the corresponding verbatim phrase include descriptions of arthralgia (such as joint pain and “achy”).

I also reviewed the Cohort 9 AE file to ascertain to what degree there was overlap between subjects who reported arthralgia and subjects who reported either flu syndrome or fever. The total number of individual reports in the dataset for these three AEs was 275 (arthralgia 181 reports, flu syndrome 70 reports and fever 24 reports). Among these I found approximately 15 subjects reporting more than one of these AEs.

An additional 47 adverse events were coded to the preferred term “joint disorder.” The corresponding verbatim terms included: degenerative disk disease, herniated disc, ruptured disc, stiffness in joint, joint effusion or swelling, and (in two cases) complaints of discomfort in a joint.⁶⁷

In the labeling for the MAO-B inhibitor selegiline, generalized ache and leg pain were each reported for one selegiline-treated subject, compared to none for placebo. However, the small number of subjects in the selegiline development program does not allow for conclusions regarding the association between these AEs and selegiline.

A possible difference in physical activity between the monotherapy and levodopa adjunct cohorts was also considered as a potential contributor to the lesser degree of arthralgia in

⁶⁷ In one of the two cases, the discomfort was noted to follow knee replacement surgery.

Cohort 2. For instance, as the subjects in the levodopa adjunct cohort (Cohort 2) had more advanced Parkinson's disease than those in the monotherapy cohort (Cohort 1), they may have been physically less active. However, the association between physical activity and arthralgia is not straightforward, and increased physical activity has also been associated with a reduced discomfort from some etiologies of arthralgia.

- **Reviewer comment:** *The substantial excess of flu-like syndrome in rasagiline-treated subjects warrants further attention than what has been provided in the NDA, and it will be recommended that the sponsor conduct further analyses. Suggestions for these analyses may include the following: creation of a case definition, reassessment of verbatim adverse events to ascertain which meet the case definition, time to onset, trends in associations with other adverse events, concomitant medication (especially amantadine) and examination of these adverse events over time with rasagiline use.*

4.6.5 Laboratory Data

Teva describes the collection and analysis of laboratory data as follows: Clinical laboratory tests (biochemistry, hematology and urinalysis) were performed at screening, baseline and termination visits, as well as throughout the study as specified by the individual study protocol (ISS 7). Hematology and biochemistry results comparing rasagiline treatment to placebo in Cohorts 1 and 2 were analyzed in two ways. First, shifts from baseline (defined as the last measurement before first study drug dose) to last observed value (LOV) for each parameter were calculated. Secondly, the number of participants with changes from normal/high to low or from low/normal to high results was tabulated (ISS 1.5.6.2). The rates of subjects exhibiting any on-treatment potentially clinically significant (PCS) results were also presented, and all cases with PCS values or out of range results were listed. A table summarizing the sponsor's criteria for PCS results is provided below. A more detailed table, presenting the PCS values as well as the predefined limits of the normal range, is provided in Attachment 9.7 of this review.

Reviewer comment: *Based upon the sponsor's description of the laboratory analysis, patients shifting from non-PCS to PCS could have presented with abnormal laboratory values at baseline.*

FDA Table 37: Potentially Clinically Significant Limits for Laboratory Values (Sponsor ISS Post-Text Table 3)

Test group	Test	Units		Lower Potentially Clinical Significant Limit	Upper Potentially Clinical Significant Limit
Hematology	Hemoglobin	g/dL	Female	10.0	-
		g/dL	Male	11.5	-
	White blood cells		10 ³ /uL	2.8	16.0
	Neutrophils		10 ³ /uL	1.5	10.0
	Platelets		10 ³ /uL	75	700
Biochemistry-Renal function	Creatinine		mg/dL	-	2.0
	Urea Nitrogen (BUN)		mg/dL	-	40
Biochemistry-Liver function	ALT (SGOT)		U/L	-	3*UNR
	AST (SGOT)		U/L	-	3*UNR
	Alkaline Phosphatase		U/L	-	3*UNR
	GGT		U/L	-	3*UNR
	Total Bilirubin		mg/dL	-	2.0
	Serum Potassium		mEq/L	2.5	5.5
	Serum Sodium		mEq/L	130	150
Biochemistry-Other	Albumin		g/dL	2.5	-
	Calcium		mg/dL	7.5	12
	LDH		U/L	-	3*UNR
	Phosphorus		mg/dL	1.5	6.0
	Serum Glucose		mg/dL	50	250
	Total Protein		g/dL	4.0	10.0

Biochemistry

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor states there was an increased percentage of subjects in the rasagiline 1 mg group compared to placebo who experienced a baseline to LOV shift from low/normal to high creatinine (4.1% [rasagiline] versus 2% [placebo]), blood urea nitrogen (BUN) (4.1% [rasagiline] versus 0.7% [placebo]), and glucose (10.1 [rasagiline] versus 4.7 [placebo]) (ISS 7.1.1).

Reviewer comment: As seen in the table in Attachment 9.7, the threshold for the upper normal range differs from that for the upper **clinically significant** range.

Teva reports that no dose response was evident for these parameters,⁶⁸ and apart from the tests listed above, the percent of subjects shifting from normal to abnormal in the rasagiline group was either similar to or lower than placebo.⁶⁹ The sponsor table summarizing these results is included in Attachments 9.8 of this review.

The sponsor states that shifts from baseline to LOV were mild for both creatinine (from 1.0-1.2 mg/dL to 1.3-1.4 mg/dL) and BUN (from 17-24 mg/dL to 25-29 mg/dL), and did not reach PCS levels (see table above). Teva states the glucose shift was also mild, with a maximum of 160 mg/dL, and occurred only in rasagiline monotherapy. Teva suggests

⁶⁸ Treatment groups for dose responses analysis in Cohort 1 included rasagiline 1 mg/day, rasagiline 2 mg/day and placebo.

⁶⁹ I reviewed Sponsor Post-Text Table 101, and verified the sponsor's ISS text information on its findings.

that the absence of similar results in Cohort 2 (levodopa adjunct) supports this as an incidental finding (ISS 7.1.3).

FDA Table 38: Number and Percent of Cohort 1 Members with PCS Biochemistry Results (Sponsor Table 61)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment			Rasagiline 1 mg (N=149)			Rasagiline 2 mg (N=146)			Placebo (N=151)		
			ALL	N	%	ALL	N	%	ALL	N	%
Liver Function	BILIRUBIN (TOTAL) (mg/dL)	> Upper Limit	148	2	1.4%
	GGT (U/L)	> Upper Limit	148	2	1.4%
	SGOT (AST) (U/L)	> Upper Limit	148	1	0.7%
Electrolytes	SODIUM (mEq/L)	< Lower Limit	148	1	0.7%	145	1	0.7%	.	.	.
Renal Function	UREA NITROGEN (BUN) (mg/dL)	> Upper Limit	.	.	.	145	1	0.7%	.	.	.
Other Parameters	GLUCOSE (mg/dL)	> Upper Limit	148	2	1.4%	145	1	0.7%	151	2	1.3%
		< Lower Limit	148	1	0.7%

The sponsor states that of the four⁷⁰ participants (from the table above) with post-baseline PCS liver function test abnormalities, three⁷¹ presented with baseline abnormalities that remained relatively stable throughout the study, while for the fourth subject the GGT value (137 U/L) just exceeded the PCS range at termination (ISS 7.1.1). The sponsor notes that two subjects with post-baseline PCS glucose also had PCS hyperglycemia at screening which was relatively stable during the study. I reviewed the data for all participants with PCS laboratory results and present selected narrative summaries in Attachment 9.10 of this review.

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

Teva states that for Cohort 2, shift analysis from baseline to LOV for biochemistry results in the rasagiline group was either similar to, or less than, placebo for most parameters (the sponsor table displaying these results is included in Attachment 9.9 of this review). An increased percentage of subjects shifting from low/normal to high calcium (2.9% [rasagiline] versus 0.8% [placebo]), alkaline phosphatase (2.4% [rasagiline] versus 1.8% [placebo]) and BUN (6.7% [rasagiline] versus 5.5% [placebo]) was seen in the rasagiline group compared to placebo (ISS 7.1.2). The sponsor notes that most of these shifts were mild (for example, 10.5-11.0 mg/dL for calcium), and none of the high values for these three analytes reached PCS levels.

Reviewer comment: *In the ISS, Teva generally presented laboratory data as shift from normal to abnormal values, or vice versa. Presentation of data as mean change from baseline to last observed value was presented within the two study reports making up Cohort 2, PRESTO and LARGO. The sponsor did not analyze the laboratory data as change from baseline to maximal value.*

⁷⁰ The five PCS liver function tests summarized in the table occurred in four participants.

⁷¹ Subjects TVP-1012/231 #205, TVP-1012/231 #703 and TEMPO #335.

FDA Table 39: Number and Percent of Cohort 2 Members with PCS Biochemistry Results (Sponsor Table 62)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients			Rasagiline 1 mg (N=380)			Placebo (N=388)		
			ALL	N	%	ALL	N	%
Liver Function	BILIRUBIN (TOTAL) (mg/dL)	> Upper Limit	375	4	1.1%	384	4	1.0%
	GGT (U/L)	> Upper Limit	375	2	0.5%	384	2	0.5%
Electrolytes	POTASSIUM (mEq/L)	> Upper Limit	375	8	2.1%	384	5	1.3%
	SODIUM (mEq/L)	> Upper Limit	.	.	.	384	2	0.5%
		< Lower Limit	.	.	.	384	1	0.3%
Renal Function	CREATININE (mg/dL)	> Upper Limit	375	3	0.8%	.	.	.
	UREA NITROGEN (BUN) (mg/dL)	> Upper Limit	375	2	0.5%	384	1	0.3%
Other Parameters	PHOSPHORUS (mg/dL)	> Upper Limit	375	2	0.5%	.	.	.
	CALCIUM (mg/dL)	< Lower Limit	375	1	0.3%	.	.	.
	GLUCOSE (mg/dL)	> Upper Limit	375	3	0.8%	384	3	0.8%
< Lower Limit		.	.	.	384	2	0.5%	

Teva reports that the frequency of post-baseline PCS biochemistry results for rasagiline 1 mg was similar to, or lower than, placebo for the majority of parameters (See table above). Of the eight rasagiline-treated subjects with post-baseline PCS elevated potassium (2.1% versus placebo 1.3%), the sponsor states that one was elevated at screening and four had single abnormalities that subsequently normalized. Post-baseline PCS high creatinine (2.1 mg/dL) and BUN (45.1 mg/dL) was seen in one subject (LARGO #41508), who entered the study at PCS level which remained essentially stable. Two patients had single creatinine abnormalities that subsequently normalized during rasagiline treatment (LARGO #41603 2.0 mg/dL, LARGO #80404 2.9 mg/dL). The sponsor asserts that two subjects with single elevated phosphorus values (LARGO #10601 7.8 mg/dL, LARGO #10602 12.2 mg/dL [reference: 2.4 to 4.5 mg/dL]) may have resulted from laboratory errors, as other abnormalities occurred simultaneously in the same specimen, including severe hypoglycemia (glucose undetectable) and hyperkalemia (6.1 mg/dL)(ISS 7.1.2).

Teva states that for both Cohort 1 and 2, AEs occurred with similar frequency in the rasagiline and placebo groups for liver function abnormalities, elevated BUN and hyperlipidemia. For Cohort 1, Teva states AEs were reported with similar incidence in the rasagiline and placebo groups for lab abnormalities as a whole, bilirubinemia, and elevated glucose (Sponsor Post-Text Table 68). For Cohort 2, the following AEs occurred at similar rates for both rasagiline and placebo groups: elevated calcium, hyperphosphatemia, hypokalemia and elevated LDH (Post-Text Table 69).⁷² In Cohorts 1 and 2, no biochemistry AE was reported for more than one rasagiline-treated subject each. The sponsor reports that for Cohort 1 and 2, no SAEs were reported for biochemistry abnormalities (ISS 7.1.2).

⁷² I reviewed ISS Post-Text Table 68 and 69, and upon general review did not find any substantial differences for any laboratory test-related AE between the rasagiline and placebo groups.

Reviewer comment: *Within the ISS and the study reports of the three pivotal trials, I did not find a description of any guidance provided to investigators on determining if laboratory abnormalities should be considered an adverse event.*

Hematology

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor states there was a higher frequency of shift from high/normal to low values for rasagiline 1 mg compared to placebo for hemoglobin (2.7% [rasagiline] versus 1.3% [placebo]), hematocrit (3.4% versus 1.3%), white blood cells (4.7% versus 2.6%), and neutrophils (6.8% versus 1.4%). Teva writes that a dose response was not demonstrated for any parameter (ISS 7.2.1).⁷³ The sponsor notes that the majority of rasagiline 1 mg subjects developing neutropenia from baseline to LOV had low or borderline low white blood cells (WBC) before rasagiline treatment. Teva reports that one subject (TEMPO #427) developed PCS leukopenia ($2.8 \times 10^3/\text{uL}$) and neutropenia ($1.2 \times 10^3/\text{uL}$) after the study start (ISS 7.2.1). The sponsor notes that two subsequent WBC/neutrophil values for this subject during the active treatment phase of the study were within normal range. I provide the sponsor table summarizing these data, and additional laboratory information for selected participants who underwent such shifts, in Attachments 9.12 and 9.13 of this review.

The sponsor notes that the increased shift from high/normal to low neutrophils in rasagiline 1 mg monotherapy was not seen with rasagiline adjunct therapy, nor was it seen in patients treated with rasagiline 0.5 mg (n=134) or 2 mg (n=132)(ISS 7.2.3).

The sponsor states that post-baseline PCS hematology results were similar for rasagiline 1 mg and placebo groups (see table below). Teva notes that except for TEMPO #427 discussed above, all the rasagiline-treated patients with post-baseline PCS leukopenia (TVP-1012/231 #502; TEMPO #279) and neutropenia (TEMPO#279; TEMPO #447) also had baseline abnormalities of these parameters (ISS 7.2.1). The sponsor states that abnormalities first noted at screening persisted post-baseline for three subjects with PCS neutrophilia as well (TEMPO #40, #134, #270). Teva reports that one subject (TEMPO #91) who developed PCS anemia (11 g/dL) had been treated for a urinary tract infection one week earlier. Three subsequent hemoglobin values for this subject during the active-treatment phase of this study were within normal range.

FDA Table 40: Number and Percent of Cohort 1 Members with PCS Biochemistry Results (Sponsor ISS Table 64)

⁷³ Treatment groups for dose responses analysis in Cohort 1 included rasagiline 0.5 mg/day, rasagiline 1 mg/day and placebo.

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment		Rasagiline 1 mg (N=149)			Rasagiline 2 mg (N=146)			Placebo (N=151)		
		ALL	N	%	ALL	N	%	ALL	N	%
WHITE BLOOD CELLS (x10 ³ /uL)	< Lower Limit	148	2	1.4%	145	1	0.7%	151	1	0.7%
NEUTROPHILS (x10 ³ /uL)	< Lower Limit	148	2	1.4%	145	1	0.7%	151	2	1.3%
	> Upper Limit	.	.	.	145	3	2.1%	.	.	.
HEMOGLOBIN (g/dL)	< Lower Limit	148	1	0.7%	.	.	.	151	1	0.7%

The sponsor states that no SAEs for abnormal hematology were reported (ISS 7.2.1). Teva notes AEs of anemia (TEMPO #413: Hemoglobin 11.2, Hematocrit 33), eosinophilia (TEMPO #324: eosinophils 9.5%), and granulocytosis (TEMPO #270: 10.4 x 10³/uL) were each reported in only one rasagiline-treated participant, and they further state that these were either chronic conditions or single occurrences that subsequently resolved. Teva notes that two rasagiline-treated patients experienced an AE of leukocytosis (TEMPO #226: 12.5 x 10³/uL, TEMPO #270: 10.4 x 10³/uL) and two experienced leukopenia (TEMPO #186: 2.9 x 10³/uL, TEMPO #300: 1.4 x 10³/uL), which Teva stated corresponded with either chronic or baseline abnormalities of these parameters for the individual participants (ISS 7.2.1.).

Reviewer comment: The sponsor comments that a number of subjects with AEs for high or low laboratory values had values that were generally high or low, respectively, throughout laboratory monitoring, including at baseline. Although this is presumably noted to suggest the contribution of baseline levels in any subsequent outlying values, it raises the concern that the percent of subjects shifting from mid-range value to a more extreme value may not be the optimum method to present laboratory data. It was unclear if subjects with outlying values, but whose values were generally high or low overall, were captured by the normal/abnormal shift tables. To avoid this uncertainty, a preferable analysis method would have been to analyze subjects with normal laboratory values at baseline and those with abnormal laboratory values at baseline separately.

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

The sponsor states that an increased percentage of rasagiline 1 mg subjects compared to placebo subjects shifted from high/normal to low values for hemoglobin (6.7% versus 4.2%) and hematocrit (7.5% versus 4.2%) (ISS 7.2.2). Dose response was assessed in comparison to the 0.5 mg group from the study PRESTO. Teva reports that the percentage of participants shifting from high/normal to low values for hemoglobin was 14.7% for rasagiline 0.5 mg, 9% for rasagiline 1 mg and 6.3% for the placebo group. Similar analysis for hematocrit demonstrated 11.7% (rasagiline 0.5 mg), 12.4% (rasagiline 1 mg) and 8.2% (placebo). Two participants (0.5%) in the rasagiline 1 mg group shifted from high/normal to low neutrophils. Both subjects were from LARGO: #50202 is discussed with the PCS values below; #80702 had screening WBC/neutrophils of 4.9/2.6 x 10³/cumm, which at termination were 3.4/1.6 x 10³/cumm (ISS 7.2.2).

Teva reported that for post-baseline PCS low hemoglobin and high neutrophils, the frequency for the rasagiline and placebo groups were similar (see table below). The

sponsor states that these participants either had screening abnormalities that shifted into PCS range, or single PCS results that subsequently resolved.

FDA Table 41: Number and Percent of Cohort 2 Members with PCS Hematology Results (Sponsor ISS Table 66)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)			Placebo (N=388)		
		ALL	N	%	ALL	N	%
HEMOGLOBIN (g/dL)	< Lower Limit	375	7	1.9%	384	8	2.1%
NEUTROPHILS (x10 ³ /uL)	< Lower Limit	375	3	0.8%	.	.	.
	> Upper Limit	375	4	1.1%	384	4	1.0%
WHITE BLOOD CELLS (x10 ³ /uL)	> Upper Limit	375	3	0.8%	384	1	0.3%
PLATELETS (x10 ³ /uL)	< Lower Limit	375	2	0.5%	384	1	0.3%

The sponsor asserts that none of the three rasagiline-treated subjects (LARGO #16211, LARGO #50202, and LARGO #90501) with PCS neutropenia developed it *de novo* after study entry. Teva states for the three participants the PCS neutropenia (range 1.3-1.5 x 10³/uL) was preceded by baseline low or borderline low WBC and/or neutrophils at screening. Teva notes that for two of the three subjects, values had normalized with subsequent testing during rasagiline treatment.

Teva states that the two participants with PCS thrombocytopenia had otherwise normal platelet counts interrupted by isolated results that were so low that the sponsor considered them to be laboratory errors (LARGO #60203 [platelets 29 x 10³/uL], #60204 [platelets 10 x 10³/uL]).

The sponsor states that in Cohort 2 AEs were reported in one rasagiline-treated patient each for granulocytosis (LARGO #21811: 12.5 x 10³/uL), leukocytosis (PRESTO #677), and anemia (PRESTO #690: Borderline low hemoglobin of 13 mg/dL at screening, which normalized at baseline to 14.3 mg/L). LARGO #41603 was diagnosed with idiopathic thrombocytopenia with platelets in the normal range at 137,000, although a previous value three weeks earlier had been 117,000. Two subjects in the rasagiline group had leukopenia: LARGO #16218 with a change of WBC from 4.5, to 3.5, and returning to 4.0 x 10³/uL while on drug; PRESTO #276 experienced a change of WBC from 5.3 to 4.6 to 4.9 to 4.0x10³/uL (ISS 7.2.2). In Cohort 2 no SAE was recorded for abnormal hematology.

Urinalysis

In the ISS, Teva did not address urinalysis results by cohort, but instead referred to the analyses within the three pivotal trials. Tables summarizing urinalysis results in the individual trials (TEMPO, LARGO and PRESTO) are provided in Attachments 9.15 of this review. Teva notes that almost all urinalysis tests were similar when compared either as termination versus baseline measurements, or rasagiline versus placebo groups (ISS 7.3).

Teva reports that hematuria was the most common laboratory-related urologic AE. However, the percentage of rasagiline-treated subjects experiencing hematuria (as assessed by urinalysis) was the same as or less than the placebo-treated participants in both of the placebo-controlled cohorts.

4.6.6 Vital Signs

The sponsor describes the collection of vital signs as follows: systolic and diastolic blood pressure and pulse were measured in supine (after five minutes) and standing (after one minute) positions at all study visits, preferably in the right arm (ISS 8). Baseline was defined as the measurement at cohort entry.

Reviewer comment: *The timing of vital signs measurement with respect to the dosing schedule was not specified in the ISS or the study protocols.*⁷⁴

Although there were no dietary restrictions in the three pivotal studies, the sponsor states as an extra precaution in case of tyramine reaction all PRESTO subjects were asked to maintain a home blood pressure (BP) diary (ISS 8). The assessment of possible tyramine reactions is addressed in a separate review by Dr. Len Kapcala.

For the two placebo-controlled cohorts, Teva analyzed vital signs by generating descriptive statistics at baseline, at last observed value⁷⁵ and the change from baseline. For the uncontrolled cohorts, Teva calculated the incidence (defined as percent of subjects) and frequency (defined as number of events per 100 PY) of patients exhibiting potentially clinically significant (PCS) results (ISS 1.5.7). The sponsor's criteria for PCS measurements are given in the following table. As requested by the FDA, two additional characterizations of potential orthostatic hypotension were added for all cohorts: (1) supine-standing SBP measurements between 20 and 29 mmHg, and (2) supine-standing SBP of 30 mmHg or over (ISS 8.1.1.1)

FDA Table 42: Potentially Clinically Significant (PCS) Vital Sign Limits
(Adapted from Sponsor ISS Post-Text Table 6)

Vital Signs Test	Criteria for Clinical Significance
Systolic BP (mmHg)	(<90 or >180) or Change from Baseline > [30] mmHg
Diastolic BP (mmHg)	(<50 or >100) or Change from Baseline > [20] mmHg
Heart Rate (bpm)	(<45 or >120) or Change from Baseline > [20] bpm
Supine-Standing SBP (mmHg)	≥ 30
Supine-Standing DBP (mmHg)	≥ 20

Reviewer comment: *Although the optimal data presentation would have separated these two, the sponsor combines tachycardia and bradycardia into one category of PCS outlier categories. Because heart rate abnormalities do not appear to be a prominent adverse events with rasagiline (or with selegiline), the current data presentation is acceptable.*

⁷⁴ TEMPO, PRESTO and LARGO

⁷⁵ Teva did not present data on change from baseline to maximal observed value for vital sign parameters.

Vital Sign Data by Cohort

Reviewer comment: AEs related to blood pressure, including a more detailed discussion of both hypertension and hypotension, are presented in Section 4.6.4 of this review.

Summary of Vital Signs

The following table summarizes changes in vital sign outlier data for the eight analysis cohorts within the ISS:

FDA Table 43: Summary of Percentage of Rasagiline-Treated Subjects with Post-Baseline PCS Vital Sign Measurements by ISS Analysis Cohort (Adapted from Sponsor Table 69 and 74; Post-Text Table 125, 128, 131, and 134; 120 Day Update ISS Post-Text Tables 49, 52 and 55)

Percent of Rasagiline Subjects with PCS Vital Signs Changes	High BP (SBP >180 or DBP>100)	Low BP (SBP<90 or DBP <50)	Pulse (<45 or >120)	Sup-Std SBP >30 mmHg Or Sup-Std DBP >20 mmHg
1. Placebo-controlled rasagiline monotherapy (Rasagiline 1 mg only)⁷⁶	2.7 (P:4.6) ⁷⁷	4.0 (P: 6.0)	6.0 (P: 4.0)	5.4 (P: 8.6)
2. Placebo-controlled rasagiline as LD adjunct (Rasagiline 1 mg only)	4.2 (P: 3.1)	7.6 (P: 5.7)	1.6 (P: 2.1)	13.4 (P: 8.5)
3. Rasagiline Monotherapy – Any Treatment Duration	7.2	10.6	10.1	17.5
4. Rasagiline Monotherapy – Long Term Treatment	8.7	14.3	13.9	23.0
5. Rasagiline with LD in Non- Fluctuating Patients – Any Treatment Duration	3.9	10.4	5.8	18.2

⁷⁶ For this table, only data from the rasagiline 1 mg group of the placebo-controlled cohorts was used.

⁷⁷ In the placebo-controlled cohorts of FDA Table 35 and 36, "P: XX" represents the percentage of placebo subjects with the PCS vital sign changes.

6. Rasagiline with LD in Non- Fluctuating Patients – Long Term Treatment	7.3	17.1	11.0	25.6
7. Rasagiline with LD in Fluctuating Patients – Any Treatment Duration	3.9	8.7	0.9	15.3
8. Rasagiline with LD in Fluctuating Patients – Long Term Treatment	4.8	9.2	0.4	17.3

FDA 37: Summary of Percent of Rasagiline-Treated Subjects with PCS Vital Sign Measurements *and Change from Baseline* by ISS Analysis Cohort (Adapted from Sponsor Table 69 and 74; Post-Text Table 125, 128, 131, and 134; 120 Day Update ISS Post-Text Tables 49, 52 and 55)

Percent of Rasagiline Subjects with PCS Vital Signs and Change from Baseline By Cohort	High BP SBP>180, or DBP>100 And Change from BL SBP>30, DBP>20	Low BP SBP<90, or DBP<50 And Change from BL SBP>30, DBP>20	Pulse <45 or >120 (bpm) And Change from BL >20
1. Placebo-controlled rasagiline monotherapy (Rasagiline 1 mg only)	0.7 (P: 0.7)	0.7 (P: 0.7)	0.7 (P: 1.3)
2. Placebo-controlled LD⁷⁸ adjunct (Rasagiline 1 mg only)*	2.1 (P: 1.3)	3.2 (P: 1.3)	0.3 (P: 0.8)
3. Rasagiline Monotherapy – Any Treatment	3.2	1.3	0.3
4. Rasagiline Monotherapy – Long Term Treatment	4.4	2.0	0.4
5. Rasagiline with LD in Non- Fluctuating Pts. – Any Treatment	3.3	4.9	1.1

⁷⁸ LD: Levodopa.

6. Rasagiline with LD in Non-Fluctuating Pts. – Long Term Treatment	5.6	8.3	0.0
7. Rasagiline with LD in Fluctuating Pts. – Any Treatment	2.0	3.5	0.5
8. Rasagiline with LD in Fluctuating Pts. – Long Term Treatment	2.8	3.2	0.4

Reviewer comment: The distinction between the analyses in the two preceding tables is that the second takes the subject's baseline status into consideration.

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor asserts that overall there are no notable differences in vital sign parameters between the rasagiline 1 mg, rasagiline 2 mg and placebo groups (rasagiline 1 mg and placebo values are provided in the summary table above). A similar percent of rasagiline-treated subjects (0.7%) and placebo-treated subjects (0.7%) in Cohort 1 experienced PCS hypertension and change from their baseline values. A likewise similar percent of the rasagiline and placebo group experienced PCS hypotension (0.7%) and change from their baseline value (table 37 above).

Teva also presented mean change from baseline to termination analyses of the vital sign data, displayed in the table below. The largest difference observed was an increase in supine-standing SBP observed in the rasagiline 2 mg group compared to 1 mg and placebo (2.9, -0.4 and -1.4 mmHg, respectively) (ISS 8.1.1.1).

FDA Table 44: Mean Vital Sign Change from Baseline to Termination for Cohort 1 (Sponsor Table 67)

Rasagiline ISS Cohort No. 1: Placebo-Controlled Studies Without Levodopa Treatment	Rasagiline 1 mg (N=149)	Rasagiline 2 mg (N=146)	Placebo (N=151)
Supine Systolic BP (mmHg) Change	0.3	-0.0	-2.3
Standing Systolic BP (mmHg) Change	0.5	-2.8	-0.9
Supine-Standing Systolic BP (mmHg) Change	-0.4	2.9	-1.4
Supine Diastolic BP (mmHg) Change	-0.4	-1.0	-1.0
Standing Diastolic BP (mmHg) Change	0.3	-1.2	-0.9
Supine-Standing Diastolic BP (mmHg) Change	-0.7	0.3	-0.1
Supine Pulse (bpm) Change	0.0	0.2	0.3
Standing Pulse (bpm) Change	-0.1	-0.1	-0.2

Reviewer comment: In interpreting the table above, I reviewed Sponsor ISS Post-Text Tables 106 to 113, which presented descriptive statistics for the parameters above at

baseline, LOV, and mean change between the two. A positive value in the table above represents an increase in the unit of measurement (mmHg or bpm) for the parameter. For example, the mean supine SBP was 127.8 mm Hg at baseline for the 1 mg group, 128.2 mm Hg at LOV, with a mean change of 0.3 mmHg. Likewise, a negative value represents a mean decrease in the unit of measurement for the parameter between baseline and LOV (for rasagiline 1 mg, standing pulse changed from 74.2 bpm at baseline to 74.1 bpm at LOV, for a mean change of -0.1 bpm.)

Using the format in the table above, it may be difficult to intuitively comprehend what the values for supine-standing blood pressure measurement represent with regards to absolute changes in blood pressure over time. To simplify the data presentation I include a table below showing the mean supine-standing values for the treatment groups:

FDA Table 45: Changes in Supine-Standing Systolic and Diastolic Blood Pressure for Cohort 1 (Adapted from Sponsor ISS Post-Text Table 108 and 111)

Change in Mean Supine-Standing Blood Pressure from Baseline to Last Observed Value	Systolic		Diastolic	
	Rasagiline 1 mg (N=149)	Placebo (N=151)	Rasagiline 1 mg (N=149)	Placebo (N=151)
Mean Supine-Standing (mmHg) at Baseline	3.2	3.8	-1.5	-1.0
Mean Supine-Standing (mmHg) at LOV	3.0	2.5	-2.2	-1.2

From the table above, the mean drop in systolic supine-standing blood pressure was essentially stable between baseline and LOV. (Of course this method of analysis does not include information on changes that may have occurred during the course of the study.) There was a slightly greater increase in diastolic supine-standing blood pressure for rasagiline 1mg subjects compared to placebo subjects.

The sponsor notes that the percentage of post-baseline PCS values was higher in the placebo group than in the rasagiline 1 mg group for all parameters except pulse <45 and >120 bpm (6.0% for rasagiline 1 mg versus 4.0% for placebo) (Sponsor Table 69). However, as the percentage of post-baseline PCS pulse outliers in the rasagiline 2 mg group (2.7%) was even lower than placebo (4.0%), the sponsor concludes that no dose-response relationship was present (ISS 8.1.1.1). The sponsor reports that only a few patients with post-baseline PCS pulse change increased >20 bpm from baseline. The sponsor therefore suggests that most patients measured as PCS at some time during the study had a change of less than 20 bpm from baseline, and were therefore relatively bradycardic or tachycardic at study entry.

Reviewer comment: Given the wide range between the extremes of normal heart rate (45-120 bpm) and the fairly stringent criteria for abnormal heart rate (ie. bradycardia as less than 45 bpm), it is possible for subjects to have changes in heart rate from baseline of greater than 20 bpm and stay within the normal limits.

For measures of postural hypotension (supine-standing), the sponsor notes that while placebo and rasagiline 1 mg were similar for differences of between 20-30 mmHg (16.6% versus 16.8% respectively), there was an increased percentage of subjects with post-baseline supine-standing SBP \geq 30 mmHg in the 2 mg group (8.9%, 4.0% and 5.3% in the rasagiline 2 mg, 1 mg and placebo groups, respectively)(Sponsor ISS Table 70 and 71).

Cohort 2: Placebo-Controlled Rasagiline Adjunct to Levodopa

Teva states that there were no notable differences in the mean values for change from baseline between the rasagiline 1 mg and placebo groups (FDA Summary Tables above, ISS 8.1.1.2). The percent of rasagiline-treated subjects in Cohort 2 experiencing PCS hypertension (2.1%) or hypotension (3.2%) accompanied by a substantial change in baseline were higher than the respective placebo groups (1.3% each).

FDA Table 46: Mean Vital Sign Change from Baseline to Termination for Cohort 2 (Sponsor Table 72)

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients	Rasagiline 1 mg (N=380)	Placebo (N=388)
Supine Systolic BP (mmHg) Change	-0.6	-0.2
Standing Systolic BP (mmHg) Change	-2.2	-0.3
Supine-Standing Systolic BP (mmHg) Change	1.6	0.2
Supine Diastolic BP (mmHg) Change	-0.8	-0.3
Standing Diastolic BP (mmHg) Change	-1.9	-1.0
Supine-Standing Diastolic BP (mmHg) Change	1.1	0.6
Supine Pulse (bpm) Change	-1.0	0.1
Standing Pulse (bpm) Change	-0.3	0.6

Reviewer comment: As per the table above, mean standing systolic blood pressure fell 2.2 mmHg from baseline (mean 124.7 mmHg) to LOV (mean 122.5 mmHg) for rasagiline 1mg, compared to a drop of 0.3 mmHg in the placebo group, and mean standing diastolic blood pressure fell 1.9 mmHg compared to 1.0 mmHg in placebo.

As with Cohort 1 above, the changes in supine-standing values are more difficult to interpret, and are presented as mean changes over time in the table below.

FDA Table 47: Changes in Supine-Standing Systolic and Diastolic Blood Pressure for Cohort 2 (Adapted for Sponsor ISS Post-Text Table 116 and 119)

Change in Mean Supine-Standing Blood Pressure from Baseline to Last Observed Value	Systolic		Diastolic	
	Rasagiline 1 mg (N=380)	Placebo (N=388)	Rasagiline 1 mg (N=380)	Placebo (N=388)
Mean Supine-Standing	4.3	3.9	-0.1	-0.4

(mmHg) at Baseline				
Mean Supine-Standing	6.0	4.0	0.9	0.2
(mmHg) at LOV				

From the table above, the mean drop in supine-standing systolic blood pressure for rasagiline-treated subjects was somewhat increased at LOV (6.0 mmHg) compared to baseline (4.3 mmHg). The supine-standing systolic blood pressure change for placebo subjects was essentially unchanged. For the diastolic blood pressure, in rasagiline-treated subjects there was a mild drop in supine-standing mean diastolic blood pressure at LOV (0.9) compared to that at baseline. The placebo diastolic was again relatively stable from baseline to LOV.

The sponsor notes that the largest difference between rasagiline 1 mg and placebo-treated subjects occurred for postural hypotension⁷⁹ (13.4% vs. 8.5%, FDA Summary Table above), which they suggest could be expected given the potential for increased dopaminergic effect of rasagiline added to levodopa and the other dopaminergic drugs which were commonly used in this population (ISS 8.1.1.2).⁸⁰ The sponsor asserts that this is reinforced by the categorical analysis of postural hypotension, in which the incidence of supine-standing SBP between 20-29 mmHg is also increased in the rasagiline 1 mg group compared to placebo (24.2% versus 20.1%, respectively), and the incidence of supine-standing SBP \geq 30 mmHg is higher in the rasagiline 1 mg group compared to placebo (10.5% versus 6.7%, respectively) (ISS Table 76).

Cohort 3: Rasagiline Treatment without Levodopa - Any Treatment Duration

The sponsor states that the frequency of post-baseline PCS vital signs for most parameters was similar to that of the placebo and rasagiline 1 mg groups of Cohort 1 (Post-Text Table 125, shown below).

Teva notes that rate of post-baseline SBP postural change \geq 30 mmHg for Cohort 3 (13.3%, 18.6/100 PYs) fell between that of the rasagiline 1 mg (4.0%, 10.9/100 PYs) and 2 mg (8.9%, 30.4/100 PYs) groups of Cohort 1 (ISS 8.1.2.1). However, the sponsor states that comparison between Cohort 1 and 3 is complicated by variation between study visit frequency for TEMPO (every month) and its open-label extension (every three months), affecting opportunity to measure vital signs (ISS 8.1.2.1).

Cohort 4: Rasagiline Treatment without Levodopa - Long Term Treatment

The sponsor states that the rate of all post-baseline PCS vital sign parameters of Cohort 4 (Post-Text Table 128 and Table 79) was similar to that of Cohort 3, suggesting no cumulative effect on vital signs with long term rasagiline monotherapy (ISS 8.1.2.2).

⁷⁹ The term "postural hypotension" used here indicates vital sign measurement meeting the criteria for postural hypotension (data presented in Sponsor ISS Table 73 and 74), and does not refer to AEs of postural hypotension, which are discussed Section 4.6.4.2 of this review.

⁸⁰ Approximately 65% of Cohort 2 participants received dopamine agonists in addition to rasagiline (ISS 8.1.2.1).

Reviewer comment: While the rates (as calculated as number of reports per 100 PYs) of post-baseline PCS values were indeed similar or slightly lower when Cohort 4 (long term treatment) was compared to Cohort 3 (any treatment duration), this is difficult to interpret (ie. When using the number of reports, instead of subjects affected, per 100 PYs, the rate for one subject with ten events and ten subjects with one event would be the same). Of note, the **percent** of subjects with PCS vital sign changes from baseline was slightly **higher** in Cohort 4 than in Cohort 3 (see FDA summary tables above).

Cohort 5: Rasagiline as Levodopa Adjunct: Non-Fluctuating Patients - Any Treatment Duration

The percentage of post-baseline PCS values and changes from baseline vital signs for Cohort 5 are provided in the FDA summary tables above (120 Day Update 6.1.1). For measurements of postural hypotension, the sponsor reports 36.1% of cohort members (38.5/100 PYs) had a supine-standing blood pressure value of between 20 and 30 mmHg, while 19.7% (26.3/100 PYs) had a value over 30 mmHg (120 Day Update 6.1.2 – tables not shown in this review).

Cohort No. 6: Rasagiline as Levodopa Adjunct: Non-Fluctuating Patients - Long Term Treatment

The percentage of post-baseline PCS values and changes from baseline vital signs for Cohort 6 are provided in the FDA summary tables above (120 Day Update 6.1.2). For measurements of postural hypotension, the sponsor reports 50% of cohort members (37.5/100 PYs) had a supine-standing blood pressure value of between 20 and 30 mmHg, while 25.9% (25.6/100 PYs) had a value over 30 mmHg (120 Day Update 6.1.2). The sponsor suggests that the similar rates of PCS vital signs parameters in Cohorts 5 and 6 indicates there is no cumulative long-term effect of levodopa added to rasagiline for this population.

Cohort 7: Rasagiline Treatment (1 mg): Levodopa-Treated Fluctuating Patients - Any Treatment Duration

Teva notes that the most common PCS change from baseline was for supine-standing SBP/DBP (32.6 reports/100 PYs), followed by low BP (13.2 reports/100 PYs) (120 Day Update 6.1.3). When postural hypotension is categorized further, changes in SBP between 20-29 mmHg occurred with a rate of 59.7 reports/100 PYs and changes 30 mmHg or over with a frequency of 25.6 reports/100 PYs (120 Day Update 6.1.3). The frequency of PCS hypertension in Cohort 7 was 6.2 reports/100 PYs (FDA summary table above). The sponsor states that the incidence of all PCS vital signs parameters for Cohort 7 is similar to that of the rasagiline 1 mg group of the placebo-controlled Cohort 2 of the original ISS (120 Day Update 6.1.3).

Cohort 8: Rasagiline Treatment (1 mg): Levodopa-Treated Fluctuating Patients - Long-Term Treatment

The sponsor states that the percentage of subjects for most post-baseline PCS parameters were similar or slightly higher in Cohort 8 (FDA summary table above) compared to Cohort 7 (120 Day Update 6.3.2), while rates in Cohort 8 for most post-baseline PCS vital signs parameters were lower than those for Cohort 7 (120 Day Update 6.1.4). Hypertension occurred with equal frequency in Cohorts 7 and 8 (6.2 vs. 6.3 reports/100 PYs). PCS high BP associated with a PCS change from baseline was slightly higher in the long-term cohort (3.4 vs. 4.0 reports/100 PYs in Cohorts 7 and 8, respectively).

Cohort 9: All PD Patients Treated with Rasagiline

The sponsor did not present vital sign data for Cohort 9.

Reviewer comment: *This is acceptable as data has been presented for all previous cohorts, which are subsets of Cohort 9, and vital sign analysis in Cohort 9 would have been complicated by the heterogeneous nature of the cohort.*

4.6.7 ECG data

Data Collection

The sponsor describes ECG collection and interpretation in the three pivotal studies as follows:⁸¹ Baseline was defined as a single tracing ECG taken at screening (before dosing). ECGs (12-lead) were then performed as per the individual study schedule in each of the PRESTO, TEMPO and LARGO studies.⁸² For TEMPO, ECGs were read by machine and confirmed by a local cardiologist at each investigating site. In PRESTO and LARGO, a centralized facility was responsible for the reading of ECGs, through a digitized algorithm with interpretation by a single cardiologist assigned to each trial.

For analysis, Teva states that three measurements of QT interval corrected for heart rate (QTc) were calculated by both the Bazett and Fridericia methods from three pairs of QT and RR intervals, and a mean of the three QTc values was taken. The sponsor states respiratory variation was not specifically addressed. The PCS absolute QTcBazett (QTcB) value was defined using the CPMP⁸³ criteria: greater than 450 msec for men and greater than 470 msec for women (ISS 9.1.2). As per the FDA's suggestion (communication, June 6, 2003), additional outlier analysis was completed for both

⁸¹ Information in this section on Data Collection was obtained primarily from a sponsor summary document of ECG methods received March 15, 2004 in response to questions from the FDA Safety Reviewer. ECG methodology was also discussed by the sponsor in the ISS and the TEMPO, PRESTO and LARGO study reports.

⁸² The sponsor states that data from unscheduled visits were also included in this analysis (ISS 1.5.8).

⁸³ Teva states that the Committee for Proprietary Medicinal Products (CPMP) guidelines suggest that a QTcB change from baseline of between 30-60 msec may represent a drug effect and raises concerns of potential cardiac risk. The sponsor characterizes changes from baseline greater than 60 msec as "a clear concern."

absolute QTcB and absolute QTcFridericia (QTcF) greater than 500 msec. Further analysis of change from baseline QTcF of greater than 60 msec was also performed (ISS 9.1.2).

Additional analyses included the calculation of descriptive statistics for heart rate and ECG intervals at baseline and at last observed value (LOV), as well as change from baseline (Post-Text Table 138).⁸⁴ Arrhythmia, myocardial infarction, rhythm, ST-T segment, T wave and U wave changes were analyzed by calculating the number of subjects changing from the normal to abnormal category or present to absent category, or vice versa as appropriate, for baseline, interim (TEMPO only) and termination (LOV) ECGs (TEMPO, PRESTO and LARGO) (ISS 1.5.8). The number of patients with a non-PCS to a PCS shift in the absolute QTc interval and vice versa between baseline and any time during the study was calculated (Post-Text Table 7)(ISS 1.5.8).

Reviewer comment: *In TEMPO, ECGs were examined at screening, Week 14, Week 26, Week 52 and Week 58. During PRESTO and LARGO, however, ECGs were performed only at screening and one subsequent visit (Week 18 for LARGO, Week 26 for PRESTO). (LARGO study report 9.6.3, PRESTO study report 7.6.2.4).*

ECG Results

Preclinical Findings

Teva assessed the effect of rasagiline on the cardiovascular system in three animal species: dogs, rats and cats. In the canine study, conscious animals acutely treated with rasagiline (3 mg/kg, oral) were monitored by telemetry. Teva states that rasagiline produced no overt treatment related changes in cardiovascular parameters during these canine studies. The sponsor also reports that rasagiline caused no effects on the cardiovascular system in cats (up to 1 mg/kg, i.v.) or rats (when administered repeatedly at doses exceeding those required for selective MAO-B inhibition (Nonclinical Overview 2.4.2.3).

No hERG channel assays were performed during the preclinical cardiac evaluation.

Cohort 1: Placebo-Controlled Rasagiline Monotherapy

The sponsor states that analysis of baseline to LOV ECG changes in Cohort 1 revealed no differences between treatment groups for the either categorical ECG parameters (described above) or for QT intervals when examined as change from normal to abnormal (ISS 9.1.1).

FDA Table 48: Analysis of ECG from Baseline to LOV for Cohort 1 (Sponsor Table 84)

⁸⁴ The sponsor stated that the Last Observed Value (LOV) was defined as the last values obtained during study (ISS 1.5.8).

Rasagiline ISS Cohort No. 1: Placebo- Controlled Studies: Without Levodopa Treatment	Last Observed ECG Result					
	Rasagiline 1 mg (N=149)		Rasagiline 2 mg (N=146)		Placebo (N=151)	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
	N	N	N	N	N	N
ECG at Screening						
Normal	60	19	66	13	60	23
Abnormal	23	45	19	42	18	43
All	83	64	85	55	78	66

Reviewer comment: *In contrast to the more detailed information provided for Cohort 2, in Cohort 1 the ECG analysis only identifies the percentage of patients with a normal ECG at baseline and then an abnormal ECG at end of study. The analysis did not specify the type of abnormality and therefore provides limited information. The TEMPO study report presents ECG data in the same manner, but provides the following narrative of a participant with an abnormal ECG finding.*

*I inquired of Teva if it would be possible to prepare a more comprehensive evaluation for Cohort 1, including an analysis of mean interval change and outliers. Teva replied that this would not be possible,85 due to differences in the TEMPO protocol and the protocol for the Cohort 2 studies PRESTO and LARGO. Teva noted that in TEMPO, a cardiologist at each investigating site assessed the ECGs, and ECG data collection consisted of categorizing the ECG as either normal or abnormal.86 Thus, more detailed information from the Cohort 1 ECGs was not immediately **available for further analysis.***

TEMPO #335: A 72-year-old woman was randomized on 22 December 1997 to rasagiline 1 mg. The subject's QTc throughout the study were as follows: *Screening:* 435 mm; *Week 14:* 450 mm; *Week 26:* 440 mm; *Week 52:* 470 mm. Six weeks after study drug discontinuation the QTc remained at 470 mm. No relevant concomitant disorders or medications were noted.

The sponsor asked a consultant cardiologist, Dr [redacted], to review this subject's ECGs. Dr. [redacted] report stated all of the participant's ECGs demonstrated mildly prolonged QTc, which he considered to be probably unrelated to treatment (TEMPO Attachments 16.2.3.11).

Cohort 2: Placebo-Controlled Rasagiline as Levodopa Adjunct

The sponsor provided descriptive statistics summarizing ECG interval and heart rate changes in ISS Post-Text Table 138. Mean heart rate for the rasagiline 1 mg was relatively unchanged from screening (71.6 bpm) to LOV (70.2 bpm). Mean PR interval

⁸⁵ E-mail correspondence from Teva with attachment, received by this reviewer on April 28, 2004.

⁸⁶ Teva reports that ECGs in TEMPO were actually coded into one of three categories: normal, abnormal but acceptable for study purposes or abnormal and unacceptable for study purposes.

(166.0 msec screening, 166.5 LOV) and mean QRS interval (92.7 msec screening, 92.9 msec LOV) likewise demonstrated little change from baseline to LOV.

The sponsor reports a mean QTcB interval change from screening to LOV as 1.1 msec for the rasagiline 1 mg group and 0.4 msec in the placebo group (ISS 9.1.2). QTcF mean interval change from screening for rasagiline 1 mg was 2.4 msec and 0.5 m sec for placebo (see table below).

FDA Table 49: Descriptive Statistics of QTc Parameters at Screening, Last Observed Value (LOV) and Change from Screening (Sponsor ISS Table 85)

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Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (phase III): Levodopa-Treated Fluctuating Patients		Rasagiline 1 mg (N=380)	Placebo (N=388)
QTc Mean Interval (Bazett) (msec) Screening Value	N	380	387
	Mean	404.1	402.8
	Std	26.0	23.2
	Min	332	326
	Max	521.0	473.0
QTc Mean Interval (Bazett) (msec) LOV	N	356	368
	Mean	404.9	402.7
	Std	25.0	24.3
	Min	337	316
	Max	513.0	474.0
QTc Mean Interval (Bazett) (msec) Change from Screening	N	356	367
	Mean	1.1	0.4
	Std	24.2	22.3
	Min	-92	-65
	Max	64.0	71.0
QTc Mean Interval (Fridericia) (msec) Screening Value	N	380	387
	Mean	393.3	392.1
	Std	23.0	20.7
	Min	334	315
	Max	517.0	463.0
QTc Mean Interval (Fridericia) (msec) LOV	N	356	368
	Mean	395.4	392.4
	Std	22.1	20.7
	Min	328	313
	Max	494.0	463.0
QTc Mean Interval (Fridericia) (msec) Change from Screening	N	356	367
	Mean	2.4	0.5
	Std	21.1	19.3
	Min	-74	-62
	Max	52.0	56.0

Shifts to PCS absolute QTcB occurred more often in the placebo group (1.9%) than in the rasagiline 1 mg group (1.4%) (see table below). When the same tabulation was done with the extension of the QTc absolute criteria to >500msec, one (0.3%) rasagiline-treated (1mg) patient (LARGO #16211) did have a treatment-emergent absolute QTcB > 500 msec, compared to none in the placebo group (ISS 9.1.2). No cardiovascular adverse

events were listed for the subject, and her AEs included hematuria, a kidney cyst and vivid dreams. Another subject who received rasagiline 0.5 mg and had an absolute QTcB > 500 msec (PRESTO #253) is discussed below.

FDA Table 50: Number and Percentage of PCS Shifts for Absolute QTcB from Baseline to Any Time During Study for Cohort 2 (Sponsor ISS Table 86)

*Females QTc>470 msec; Males: QTc>450 msec

Rasagiline ISS Cohort No. 2: Placebo-Controlled Studies (phase III): Levodopa- Treated Fluctuating Patients	Rasagiline 1 mg (N=380)		Placebo (N=388)	
	N	%	N	%
Shift of PCS QTc Results				
Non PCS to Non PCS	347	96.9	356	97.0
Non PCS to PCS	5	1.4	7	1.9
PCS to Non PCS	3	0.8	4	1.1
PCS to PCS	3	0.8	.	.
All	358	100.0	367	100.0

**Unscheduled visits data was included

Teva asserts there were no notable differences in the descriptive statistics for categorical ECG parameters between the rasagiline 1 mg and placebo groups. The sponsor states shift analysis from baseline to LOV for the categorical data was also similar between the two groups, with the exception of a higher percentage of rasagiline-treated subjects (2.9% versus 1.0%) changing from normal to abnormal T waves (ISS 9.1.2).

For the two studies comprising Cohort 2, in PRESTO AEs were recorded for flattening of T waves for two participants: PRESTO #38 for ST depression, and PRESTO #219 for ECG changes following a recent pulmonary embolism. Another subject (PRESTO # 272) was observed to have ST depression at termination, although the sponsor noted the participant had undergone coronary bypass surgery several months prior (PRESTO Study Report). Teva notes that all of these subjects completed the study. SAEs were recorded for atrial flutter (PRESTO # 371), worsening bradycardia/sick sinus syndrome (PRESTO# 472) and ventricular tachycardia (PRESTO # 253). PRESTO #253 had an absolute QTcB and QTcF >500 msec at termination as well as change from baseline of > 60 msec for QTcB and QTcF. Teva notes that his termination ECG was an artificial pacemaker rhythm, compared to sinus rhythm at screening, which made the shift difficult to assess.

Reviewer comment: The narrative for PRESTO #253 reports that the subject discontinued the study drug due to the serious adverse event of ventricular tachycardia, and notes artificial pacemaker rhythm on termination ECG (two months after rasagiline was discontinued). However, it was not specifically mentioned in the narrative or among the subject's listing of adverse events that a pacemaker had been inserted during the trial

(PRESTO study report pg. 433 and pg. 533). A request will be forwarded to Teva to clarify whether a pacemaker was indeed inserted.

For LARGO, two rasagiline-treated participants shifted from myocardial infarction absent to present. LARGO # 90112 presented at the termination visit with septal Q waves and was diagnosed with "subclinical infarction." LARGO # 50506 had two ECGs performed prior to receiving the study drug, the first showing septal infarction and the second not demonstrating this. The termination ECG was read as a "new" infarction in comparison to the second pre-drug tracing (LARGO 12.2.6). Another rasagiline-treated subject, LARGO #70702, was detected to be in atrial fibrillation during a study ECG.

4.7 Drug Demographic Interactions

The sponsor states that because the majority (95%) of participants in the rasagiline development program were Caucasian, subgroup analysis was performed for age and gender only (ISS 6.4). Teva presented this data for placebo-controlled cohorts only.

4.7.1 Sex

Cohort 1 (Placebo-controlled rasagiline monotherapy): Teva reports that most AEs with apparent sex differences demonstrated comparable variation in the rasagiline and placebo treatment groups, which they suggest is not indicative of a drug relation (ISS 6.4.1.1).⁸⁷

Cohort 2 (Placebo-controlled rasagiline as levodopa adjunct): The sponsor states that analysis by gender demonstrated a slightly higher incidence of postural hypotension, weight loss, dyskinesia and hallucinations in rasagiline-treated females (ISS 6.4.1.2).

FDA 44: Number and Percent of AEs by Sex in Cohort 2 (Adapted from Sponsor Post-Text Table 80)⁸⁸

Adverse Event	Rasagiline 1 mg (N=380)				Placebo (N=388)				Relative Risk*	
	Female (N=127)		Male (N=253)		Female (N=152)		Male (N=236)		Female	Male
	N	%	N	%	N	%	N	%		
Postural Hypotension	8	6.3	10	4.0	2	1.3	3	1.3	4.9	3.1
Weight loss	8	6.3	8	3.2	2	1.3	4	1.7	4.9	1.9
Dyskinesia	15	11.8	24	9.5	9	5.9	16	6.8	2.0	1.4
Hallucinations**	6	4.7	5	2.0	1	0.7	7	3.0	6.7	0.67

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

⁸⁷ I reviewed the stratified AEs in the sponsor's ISS Post-Text Table 77 (Cohort 1) and 79 (Cohort 2) for age, and Post-Text Table 78 (Cohort 1) and 80 (Cohort 2) for gender.

⁸⁸ For the age- and sex-stratified data, the AEs I selected from the respective sponsor tables to include in the tables in section 4.8 are those I found to differ on the stratified variable on general review, or those discussed by the sponsor in their text.