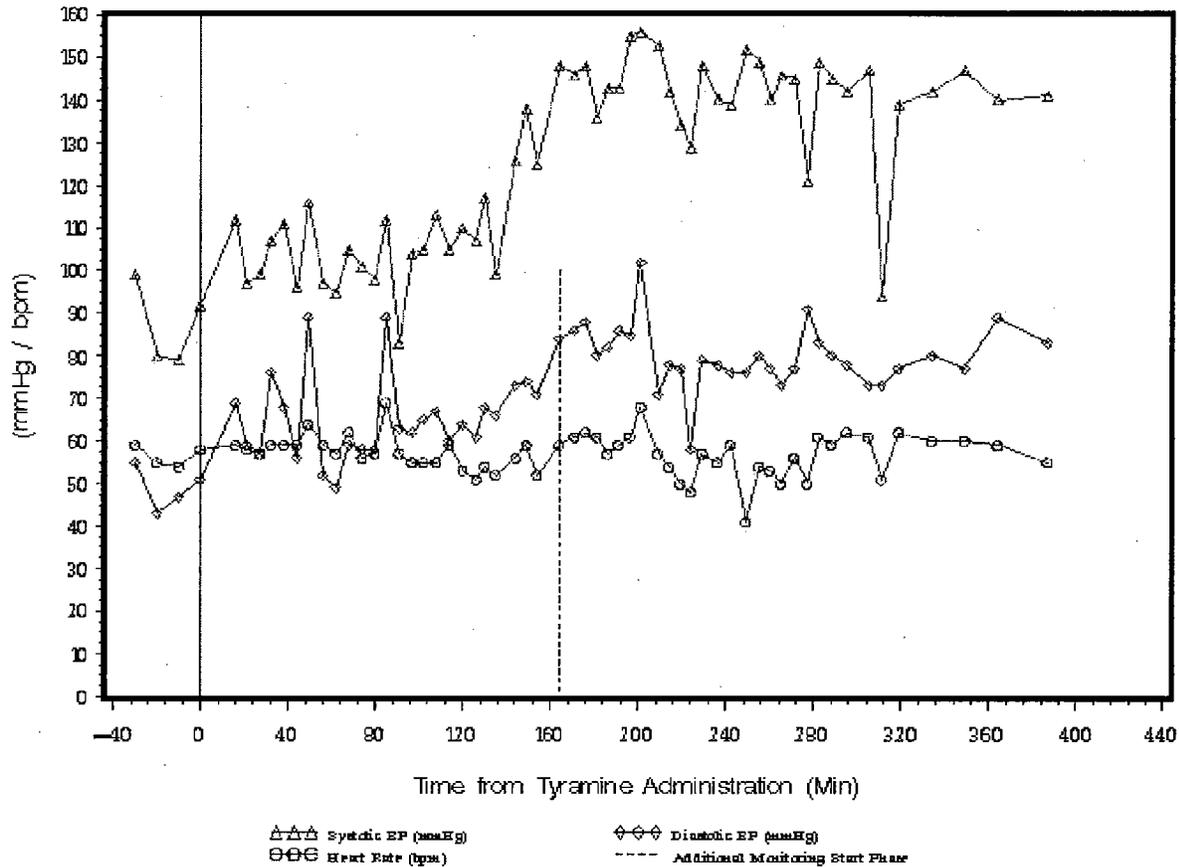


CLINICAL REVIEW

The subject performed multiple home blood pressure measurements before and after meals, during TVP-1012/133. No events of significant increase in post-meal blood pressure were recorded.

Figure 18 Vital Sign Changes Over Time in Patient # 266 (0.5 mg Rasagiline) After 50 mg Tyramine



Patient # 411 (Placebo)

This patient had fluctuations in his blood pressure. The mean baseline blood pressure was 94/57 mmHg, the mean baseline heart rate was 72 bpm. Supine blood pressure on that day (termination visit) was 136/87 mmHg. Blood pressure measurement at time of tyramine ingestion was 104/65 mmHg. About 100 minutes after tyramine administration systolic blood pressure increased from 115/65 to 130/80 (Figure 19).

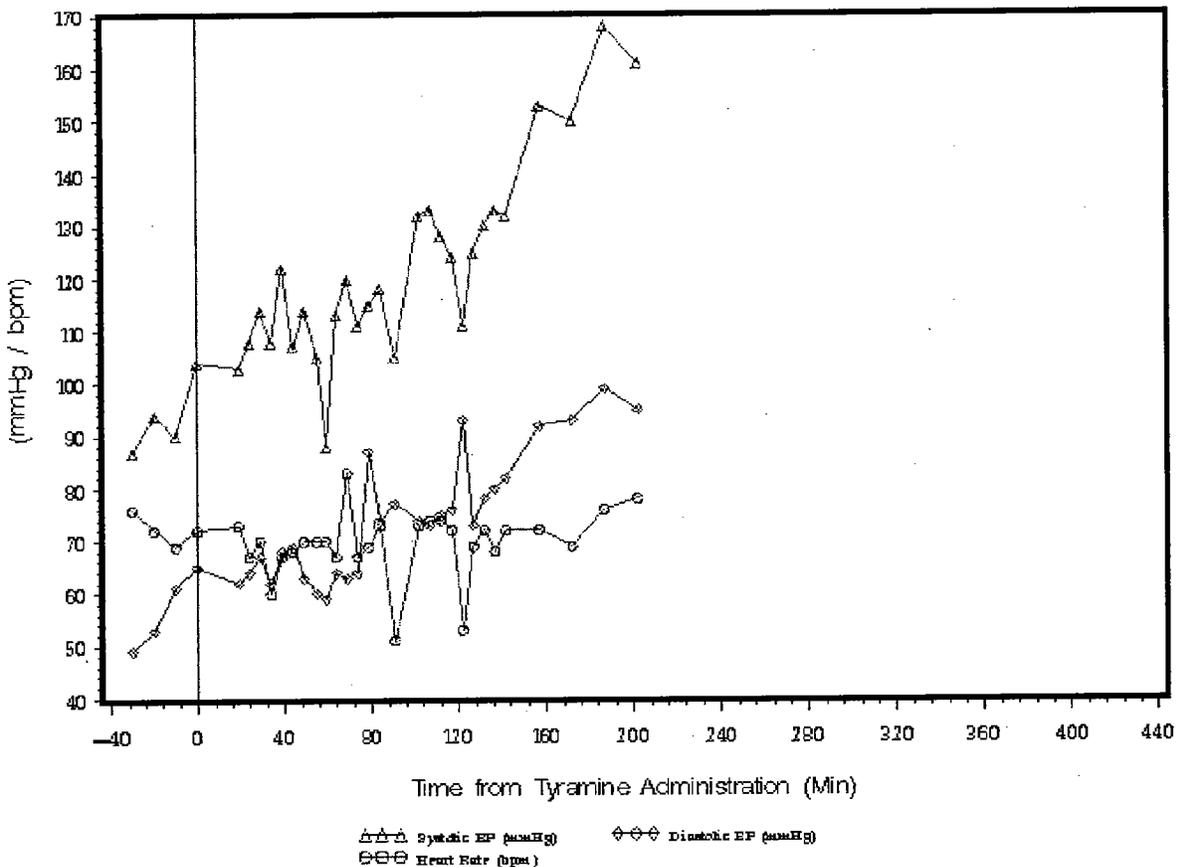
Another increase in blood pressure to 158/95 (average of last 4 measurements) occurred after another 155 minutes. The blood pressure further increased up to 168/99. Last measurement was taken 202 minutes after tyramine administration.

Heart rate did not change except for two non-consecutive measurements of 51 and 53 bpm, 90 and 120 minutes after tyramine administration.

CLINICAL REVIEW

The patient tended to be very nervous and at the time of the sub-study, the dyskinesias were not well controlled. While additional monitoring beyond the 202 minutes was not performed, a BP reading was taken after one hour and 10 minutes and it is noted in patient source documents as 102/60. The investigator believed that the increase in BP was due to difficulty to control dyskinesias. The subject performed multiple home blood pressure measurements before and after meals, during TVP-1012/133. No events of significant increase in post-meal blood pressure were recorded.

Figure 19 Vital Sign Changes Over Time in Patient # 411 (Placebo) After 50 mg Tyramine



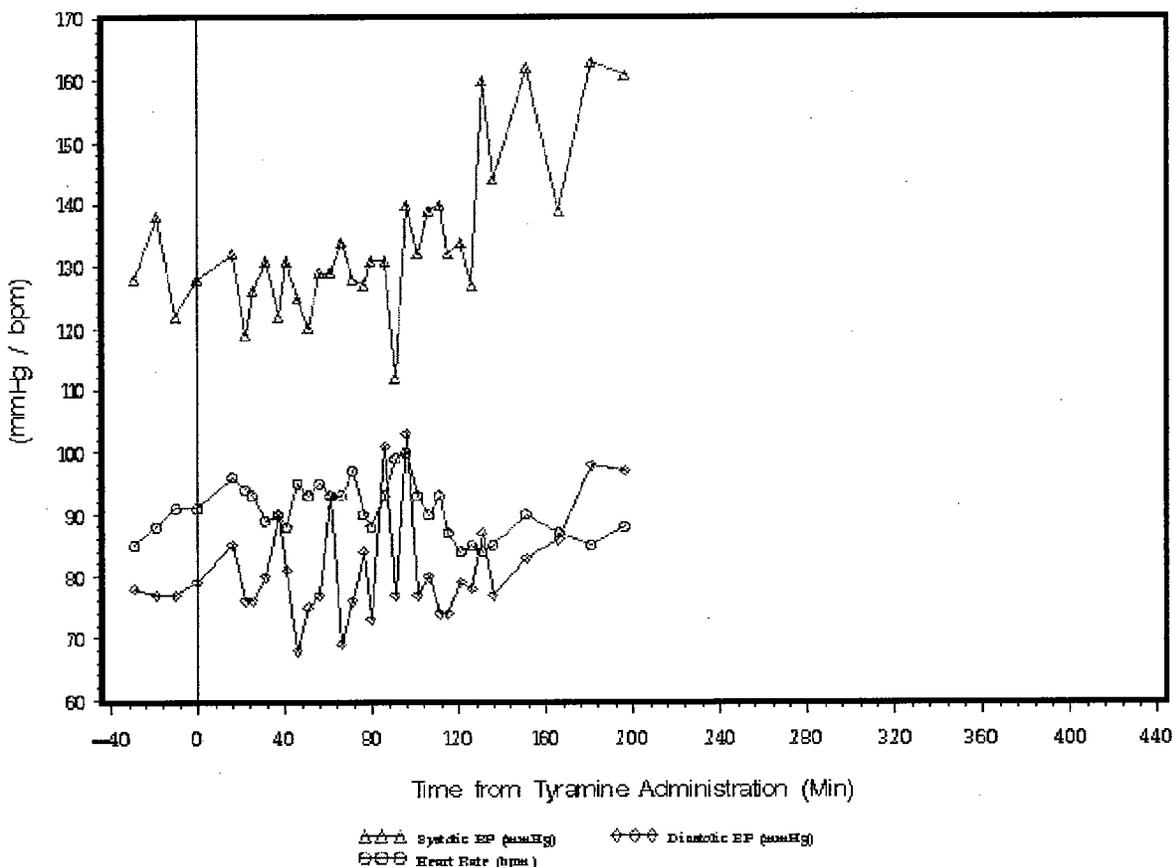
Patient # 362 (Placebo)

Between 130 and 195 minutes after tyramine administration there were 3 non-consecutive occasions of increase in systolic blood pressure of about 30 mmHg (to 163 mmHg) (Figure 20). Between measurements the BP resumed normal levels with measurements of about 140 mmHg. There was no significant change neither in diastolic blood pressure nor in heart rate.

Subject became anxious towards the end of the study and wanted to leave as ride was waiting and had a distance to travel home. Subject was released as totally asymptomatic throughout study. No events of BP elevations were recorded during home monitoring.

CLINICAL REVIEW

Figure 20 Vital Sign Changes Over Time in Patient # 362 (Placebo) After 50 mg Tyramine

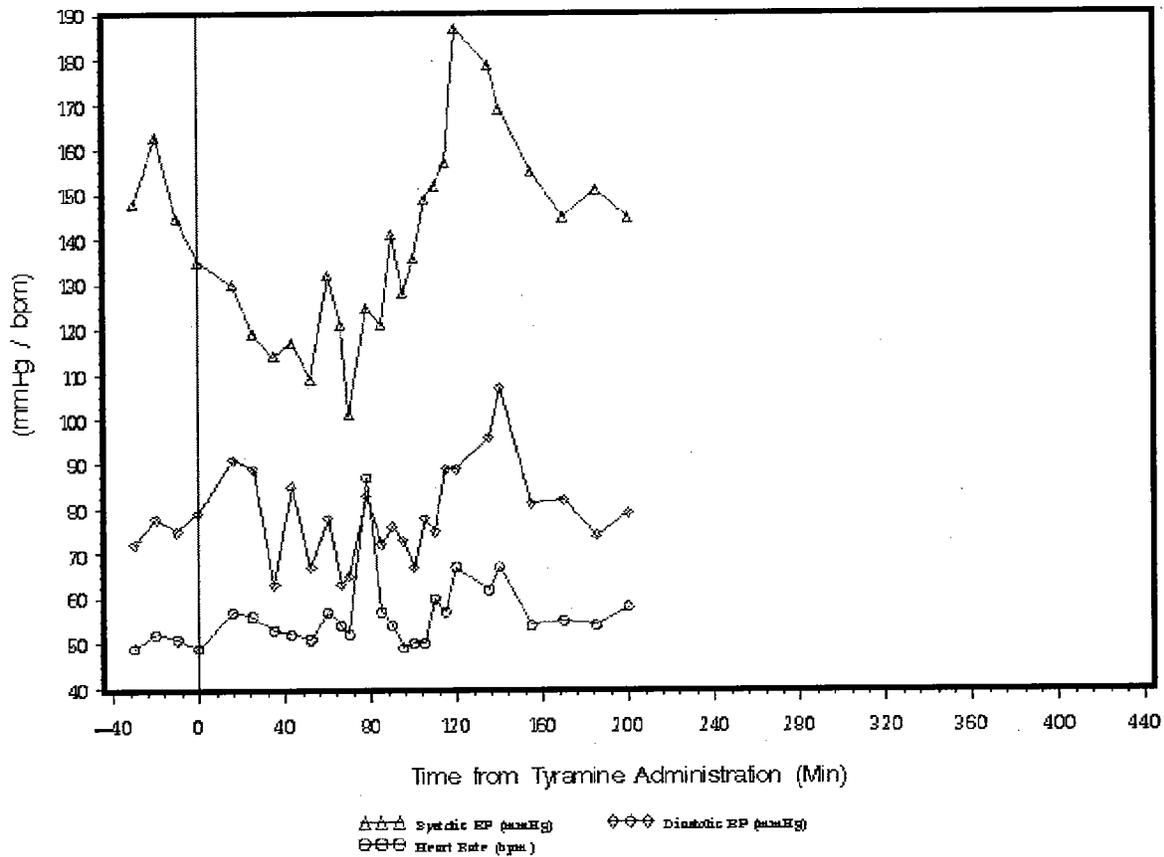


Patient # 736 (Placebo)

The mean baseline blood pressure was 148/76, 35 minutes after tyramine administration, a significant decrease of over 30 mmHg in systolic blood pressure occurred. The decrease sustained for 45 minutes. Systolic blood pressure then, increased to a peak of 187 mmHg 120 minutes after tyramine ingestion, while the patient had to use the restrooms. The BP increased over 25 minutes from 128 to 187 mmHg, and lasted for 50 minutes until resumed baseline levels (Figure 21). The BP decreased following voiding. Diastolic blood pressure increased and decreased as well, peaking 107 mmHg 20 minutes after systolic peak (minute 140). During these blood pressure changes there was no significant change in heart rate. The subject performed multiple home blood pressure measurements before and after meals, during TVP-1012/133. Several increases in BP were recorded at baseline as well as after meal.

CLINICAL REVIEW

Figure 21 Vital Sign Changes Over Time in Patient # 736 (Placebo) After 50 mg Tyramine



Decreases in Heart Rate < 40 bpm

There were no subjects in any treatment group whose heart rate fell below 40 bpm in three or more consecutive measurements taken over 10 minutes. There were no subjects who reached the endpoint related to reduced heart rate.

Table 42 Distribution of Patients with Bradycardia*

TVP-1012/133 Tyramine Sub-Study	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
All	22	100.0	13	100.0	22	100.0	57	100.0
No Bradycardia	22	100.0	13	100.0	22	100.0	57	100.0

* Measured in Heart Rate < 40 bpm Documented by at Least 3 Measurements
 Cross-Reference: Tyramine Challenge – All Vital Sign Measurements in Appendix 16.2.6.24

CLINICAL REVIEW

Secondary Outcome Measures

12-lead ECG Changes

None of the 49 subjects had a clinically significant change in the ECG following tyramine ingestion.

3-lead ECG Changes

Any subject who had an elevation of systolic BP > 30 mmHg above the mean baseline value, or a reduction in heart rate below 40 beats per minute lasting 10 minutes or more, or who reported symptoms consistent with a severe increase in BP (e.g. an AE of headache) had BP and heart rate measured every five minutes until the cardiovascular changes or adverse events resolved, for a minimum of 120 minutes after the onset of the reaction. BP and heart rate continued to be measured every 15 minutes for 60 additional minutes. A continuous 3-lead ECG was to have been recorded during this period. The total duration of observation was at least 180 minutes after tyramine administration.

Four subjects had 3-lead ECG recorded. Two (# 4 and 266) were in the group that had received rasagiline 0.5 mg/day and met the primary outcome, and there was one each in the 1mg (#. 276 had blood pressure fluctuations) and placebo (# 365 had heart rate fluctuations) groups. None of these 4 subjects had any clinically significant changes in the 3-lead ECG.

Need for Antihypertensive Therapy

No subjects required antihypertensive therapy during this sub-study.

Adverse Experiences

AEs were reported by a total of 6 subjects, all of whom had received rasagiline in PRESTO (Table 43). These 6 subjects correspond to the same 6 who were noted to have required additional cardiovascular monitoring of these AEs were serious and none required corrective drug therapy.

Table 43 Incidence and Frequency of Adverse Experiences by Body System and COSTART Term - Tyramine Sub-Study

TVP-1012/133a Tyramine Sub-Study		0.5 mg (N=22)			1 mg (N=13)			Placebo (N=22)		
		No of Reports	No. of Subjects	% of Subjects	No of Reports	No. of Subjects	% of Subjects	No of Reports	No. of Subjects	% of Subjects
-ALL	-ALL	9	5	22.7	1	1	7.7	.	.	.
Body as a whole	-ALL	1	1	4.5
	Infection	1	1	4.5
Cardiovascular system	-ALL	7	4	18.2	1	1	7.7	.	.	.
	Hypertension	6	4	18.2	1	1	7.7	.	.	.
	Palpitation	1	1	4.5
Nervous system	-ALL	1	1	4.5
	Paresthesia	1	1	4.5

Cross-Reference: Data Listing of All Adverse Experiences in the Tyramine Sub-Study Appendix 16.2.6.27

CLINICAL REVIEW

Individual Subject Data for Notable Responses

Table 44 identifies those subjects who had vital signs changes that resulted in either additional cardiovascular monitoring, 3-lead ECG recording or a subject narrative.

Table 44 Identification of Subjects with Notable Cardiovascular-related Findings

Treatment group	Subject No.	Narrative present	Per CRF		Comments
			3-lead ECG	Additional CV monitoring	
0.5	4	X	X	X	Met criteria for significant increase in systolic BP
0.5	10			X	Additional CV monitoring done because of erratic BP, not for tyramine interaction
0.5	118	X		X	Met criteria for significant increase in systolic BP
0.5	266	X	X	X	Met criteria for significant increase in systolic BP
0.5	361	Not needed		X	Did not meet criteria for additional CV monitoring, Nevertheless, for heart rate =51 bpm, and cardiac history of intermittent tachycardia, additional monitoring was done at Investigator's discretion
1.0	276	X	X	X	Met criteria for additional CV monitoring, but BP elevation was related to voiding episodes, not a tyramine-like reaction.
placebo	362	X			*Identified before unblinding as just missing predefined criteria for for significant increase in systolic BP
placebo	365	Not needed	X		No BP changes associated with tyramine, but variable heart rate led to additional monitoring done at Investigator's discretion
placebo	411	X			Met criteria for significant increase in systolic BP
placebo	736	X			*Identified before unblinding as just missing predefined criteria for for significant increase in systolic BP
No. subjects	10	7	4	6	

* Subject's BP did not quite reach criteria for Significant BP increase, however pattern of BP change was consistent with tyramine interaction: gradual rise in systolic BP to nearly 30 mmHg above baseline occurring at about 2 to 3 hours after the tyramine bolus.

Cross-Reference: Tyramine Challenge – All Vital Sign Measurements in Appendix 16.2.6.24

Cross-Reference: Tyramine Challenge – 3-Lead ECG Measurements in Appendix 16.2.6.26

8.5.3. Sponsor's Discussion and Conclusions – Tyramine Sub-study

During the course of this sub-study, four subjects had systolic BP elevations that met the pre-defined criteria of the primary outcome measure: Increase in systolic BP of > 30 mmHg above the mean baseline value, occurring in at least 3 consecutive measurements. All four subjects were asymptomatic throughout the sub-study and the BP increases did not require intervention. Three of the 4 subjects had received rasagiline 0.5 mg/day in PRESTO and one had received placebo. As no BP elevations occurred in the rasagiline 1 mg/day treatment group, the BP responses was apparently not dose-related and therefore, may not be rasagiline-related.

Before unblinding, and for consistency with the tyramine interaction substudy conducted as part of the rasagiline monotherapy trial, TVP-1012/232 (TEMPO), subjects who “just missed” the

CLINICAL REVIEW

significant BP elevation criteria were identified. There were two subjects in the “just missed” category, both treated with placebo in PRESTO. This brought the count of subjects meeting or nearly meeting the significant BP elevation criterion to 3 receiving rasagiline 0.5 mg/day (14%) and 3 receiving placebo (14%).

Since significant BP elevations meeting [or nearly meeting] the predefined criteria occurred in the placebo treatment group, there is evidence that the occurrence of significant BP elevations following a tyramine challenge does not always represent a rasagiline-tyramine interaction. Therefore, since the ratio of rasagiline-treated subjects to placebo-treated subjects in this substudy was 1.6 : 1, there was an increased probability of random BP events occurring in the rasagiline treatment groups that were not necessarily related to MAO-B inhibition.

In conclusion, although six subjects had blood pressure increases that may appear to reflect a potential rasagiline-tyramine interaction, most were eventually recognized as due to various other causes. Moreover, significant BP events were evenly distributed between rasagiline - and placebo treatment groups, with no rasagiline dose-relationship observed.

As noted in previously, 22/164 (13%) patients from the 0.5 mg rasagiline treatment group prematurely withdrew from the study out of which 15 withdrew because of AEs, 17/149 (11%) patients from the 1 mg rasagiline treatment group prematurely withdrew from the study out of which 9 withdrew because of AEs, and 19/159 (12%) patients from the placebo treatment group prematurely withdrew from the study out of which 8 withdrew because of AEs.

The Chi-Square test shows no statistically significant differences between the treatment groups in the percent of early discontinuations ($p = 0.8535$), nor in the percent of early terminations due to AEs ($p = 0.3086$).

The Log-Rank Test to compare the time to premature discontinuation shows no statistically significant differences between the treatment groups ($p = 0.2235$).

Overall it can be concluded that both the 0.5 mg/day and the 1 mg/day doses of rasagiline are well tolerated.

8.5.4. Reviewer's Comments

- I consider the lack of significant blood pressure responses after tyramine administration in most rasagiline-treated patients to be of indeterminate significance because of the potential confounding effects of administering tyramine with food (e.g. applesauce) and relatively soon after a meal). I have outlined my many reasons for concern about food altering the plasma tyramine profile and corresponding pressor response in the Reviewer's Comment section of my review of tyramine challenge Study 132.
- The study permitted the potential for additional heterogeneity of pressor responses because there was no standardized meal given to all patients. Patients were supposed to bring their own meal from home bar as long as the food met the low tyramine content restrictions. In addition, the tyramine was then administered with different dessert foods (yogurt, frozen

CLINICAL REVIEW

yogurt, or ice cream) at the end of the meal. I consider this design as potentially contributing to the possibility of different plasma tyramine profiles related to the specific, different meals among different subjects and then different foods to which tyramine was added. There are no data to show that even in the absence of a preceding meal (that was ingested by all subjects), tyramine absorption and the plasma tyramine profile is similar. Increasing differences and alterations of the plasma tyramine profile can contribute to increasing differences in the pressor response to the same amount of tyramine administered with these different desserts.

Considering that food can delay the plasma tyramine T_{max} and the corresponding pressor response, it is possible that some hypertensive reactions could have been missed if they occurred after 3 hours. In the absence of a significant cardiovascular reaction within 3 hours after administration of tyramine, blood pressure monitoring would cease and patients could be discharged. Conceivably some patients could have experienced threshold hypertensive reactions after 3 hours or their threshold responses might not have been detected by less frequent monitoring of vital signs every 15 minutes between 2-3 hours (in contrast to monitoring every 5 minutes during the first 2 hours).

- I also note that my concern about the sponsor's approach of administering tyramine just before (as in this study) or after a meal potentially confounds blood pressure responses because absorption of tyramine is not rapid and immediate. I believe that the shape of the plasma tyramine curve could be significantly altered even if tyramine was administered as a capsule and not sprinkled on food. Based upon my review (of the publication by Berlin et al. - cited previously) of the shape of pattern of the plasma tyramine curves on "average," most tyramine absorption appears to occur over approximately 1.5 hours when administered in the fasting state and this period of absorption increases to approximately 3 hours when tyramine is administered with a meal. Thus, it would be best that no food be given without several hours before or after tyramine to exclude the possibility that plasma tyramine PK was altered and correspondingly a pressor response to that amount of tyramine.
- Table 31 from the publication by Audebert et al. (1992) shows how many peak pressor responses were delayed beyond 180 minutes in subjects administered tyramine with different types of meals. It is also possible that patients may not have met the threshold of 3 consecutive hypertensive measurements at the defined threshold over 3 consecutive measurements when the monitoring frequency between 2 and 3 hours had decreased from 5 minute intervals during the first 2 hours to 15 minute intervals over the last hour (i.e. hour 2-3 post tyramine).
- In response to my request, the sponsor provided additional analyses of individual maximal systolic blood pressure and maximal systolic blood pressure increment above pre-tyramine systolic blood pressure and mean data according to treatment group for these 50 mg tyramine challenges. These analyses showed that the mean maximal systolic blood pressure was similar (141-146 mm Hg) among all treatment groups. However, the mean maximal systolic blood pressure increment above pre-tyramine baseline was higher in the 1 mg rasagiline group (27 mm Hg) than the mean value (21 mm Hg) for both the placebo and 2 mg rasagiline groups. Although the frequency of maximal systolic blood pressure increments was similar (17 - 24 %) among all treatment groups for increment \geq 30 mm Hg, there appeared to be an increased frequency of marked outlier responses \geq 60 mm Hg for the 0.5 mg rasagiline group

CLINICAL REVIEW

(18 %) compared to the placebo (5 %) and 2 mg rasagiline (0 %) groups. Although these data suggested a potentially concerning increased tyramine sensitivity associated with 0.5 mg daily rasagiline treatment, it was not clear why this apparently increased sensitivity to tyramine was not exhibited by patients treated with the higher dose of rasagiline (i.e. 1 mg). More specifically, the marked outlier responses in the 0.5 mg rasagiline group were exhibited by the 3 patients (patient # 4 - 69 mm Hg; patient # 118 - 78 mm Hg; patient # 266 - 69 mm Hg) who met the protocol-defined primary tyramine threshold outcome plus another patient (# 10 - 65 mm Hg) who did not. The single placebo patient (# 411) who exhibited a marked outlier increment patient (74 mm Hg) had also met the protocol-defined primary tyramine threshold outcome.

- It was not clear why the 3 patients treated with rasagiline (0.5 mg daily) experienced threshold pressor responses and no patients treated with 1 mg daily experienced such responses. It is conceivable that they may have experienced this reaction because their PK exposure (i.e. plasma rasagiline AUC) was increased for what was expected in patients who are given this dose and the exposure of these 3 may have been even greater than what would normally be expected in patients given 1 mg daily. The sponsor did not provide any PK data for these patients to provide any insight about this issue.
- I have noted my concerns about the biological potency for tyramine in Study P94159 because the majority (18/29) of subjects exhibited a pressor threshold response at 800 mg or did not exhibit a threshold response. This is extremely unusual. The sponsor used tyramine from the same supplier () for this study. Thus, the possibility exists that results observed in this study could underestimate the tyramine sensitivity if the tyramine used had a decreased potency than that which is normally expected.

8.5.5. Reviewer's Conclusions

- **The potentially confounding effect of administering tyramine with food (i.e. applesauce) and also eating a few minutes after this does not allow one to draw any conclusions about the effect of tyramine exposure on blood pressure response in patients treated with 1 or 2 mg rasagiline daily. It is not possible to know whether the lack of significant pressor responses in most patients administered tyramine in this study design is a true negative or potentially a false negative because of the impact of the food on the plasma tyramine profile and corresponding pressor response.**
- **The sponsor has not validated its approach of assessing tyramine sensitivity (i.e. pressor responses after tyramine) when tyramine is administered with food and immediately before other food.**
- Based upon a variety of studies in the literature, there is clear evidence that food can markedly alter the plasma tyramine profile by diminishing C_{max} , AUC, and delaying T_{max} and also the pressor response to this altered plasma tyramine curve.

CLINICAL REVIEW

- The results suggested the possibility that some patients treated with 0.5 mg rasagiline exhibited increased sensitivity to tyramine for hypertensive responses. It was not clear why similar responses were not observed in the 1 mg rasagiline group.
- The study design employed may have missed some tyramine-induced hypertensive reactions meeting the primary outcome measure and occurring relatively late (e.g. between 2-3 hours or after 3 hours) because of the confounding effect of food on the time to the response.
- It is not possible to know whether the tyramine used in this studied had a lower biological potency than that which is normally expected. If the biological potency of tyramine was diminished, results of this study may be an underestimate of the risk for rasagiline-induced tyramine sensitivity.

9. FDA BIORESEARCH MONITORING PROGRAM INSPECTIONS

There were 2 inspection reports provided by the Division of Scientific Investigation (DSI). This Clinical Inspection Summary Report (4/7/04) was prepared by Dr. Ni Khin. This inspection report was applicable to inspections at 2 sites for the TEMPO monotherapy trial and for 2 sites for 1 site for the adjunctive treatment trial. In addition, this report summarized the findings of inspections of 2 sites that participated in the pivotal trials and also a tyramine challenge substudy. A second inspection report was provided for the inspection of the single site at which the most important tyramine challenge study (Study TVP1012-P94159) was conducted.

Summary of Sites for Pivotal Efficacy Trials and Tyramine Challenge Substudies

For the study sites that were inspected (Table 45), there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted based on the limited numbers of the study subjects' records inspected. . No major concerns nor problems were identified at any of these sites. Overall, data from these centers that had been inspected appear acceptable for use in support of this NDA.

CLINICAL REVIEW

Table 45 Summary of Sites and Investigators Inspected by DSI

NAME	Protocol (Site #)	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
Andrew Feigin, M.D.	232: TEMPO and substudy (site 55)	Manhasset, NY	12/15/2003	02/09/2004	NAI
Howard Hurtig, M.D.	232: TEMPO (site 18)	Philadelphia, PA	12/15/2003	03/04/2004	VAI
Amy Colcher, M.D.	133: PRESTO (site 18)	Philadelphia, PA	12/15/2003	03/04/2003	NAI
Andrew Siderowf, M.D.	133a: substudy (site 18)	Philadelphia, PA	12/15/2003	03/04/2004	NAI
Sponsor: Teva Neuroscience	133, 133a and 232	North Wales, PA	02/05/2004	03/08/2004	NAI

Summary of Site for Study TVP1012-P94159 (Paris) Assessing Tyramine Sensitivity Under fasting Conditions

This single site in Paris that conducted the important tyramine pharmacodynamic study was inspected.

This study was conducted by _____ retired several years ago and was not present during the inspection. Instead, _____ (co-investigator) provided relevant information. Following the inspection (5/3-7/04), Form FDA 483 was issued. The main objectionable findings and of this evaluation are :

1. "There are no records of the foods consumed by the study subjects during their study participation, to document that the food restrictions in the protocol were complied with.

The clinical site stated that subjects consumed _____ "standard meals" that did not contain foods restricted by the protocol. However, records (e.g., a menu for the meals) were not maintained to document the composition of these meals, especially for biogenic amines. Furthermore, while the co-investigator claimed that the protocol was followed with regard to fasting requirements, the site only provided the case report form (CRF) to support this claim. The CRF contained a statement to verify that subjects were on an empty stomach since 2100 hours the day before, but the actual time of the previous meal was not recorded. Also, pre-printed information on the CRF concerning the meals (e.g., on day 8, no breakfast, lunch at 6 hours, dinner at 12 hours) does not confirm when meals were actually served. It should be noted that subjects were confined to the clinical unit during dosing periods."

2. "Lab reports from the contract (clinical) laboratory were not signed or initialed and dated by study physicians, documenting their review of same in a timely manner."
3. "For numerous blood pressure readings, the actual time of measurement was not recorded. For those instances where the actual time of measurement was recorded, there is no documentaion that the times of measurement were 100% audited to assure compliance with the protocol.

CLINICAL REVIEW

Blood pressure (BP) was measured either manually or by a BP machine. The co-investigator stated that, in general, automated measurements were taken during the tyramine challenge on days 8-10. Manual BPs were recorded directly on the CRF that was preprinted with protocol-defined intervals; the actual time of the manual BP readings was not documented. Furthermore, while the BP machine recorded actual times, the site did not confirm that the time of the automated readings conformed to the protocol-required collection times (e.g., every five minutes from 0.5-3 hours post-dose on day 8)."

The following are the conclusions of this inspection.

1. **"The site lacked documentation of the actual foods consumed by the subjects during study participation. Furthermore, while the site claimed that protocol requirements regarding fasting conditions were met, the CRF was the only document provided to support this claim. As described above (item 1), the CRF did not record the actual time when fasting started and ended. In light of these findings, there is no written assurance that fasting or dietary restrictions were met."**
2. **"There is no assurance that blood pressures were taken at the times defined by the protocol in that the site failed to document the actual times of manual measurements, and did not verify that automated measurements conformed to the protocol defined times (item 3 above). The medical officer should evaluate whether the unscheduled, minute by minute blood pressure measurements may have biased the outcomes."**

Reviewer's Comments

One would expect and hope that this study was conducted according to the protocol with respect to fasting and dietary restrictions and measurements of blood pressure (especially related to automated blood pressure readings during the tyramine challenges), it appears that there was no appropriate documentation to assure that the study was conducted according to the requirements outlined in the protocol. In addition, it appeared that there was unscheduled additional monitoring that was conducted subjectively when the blood pressure was "close" to the threshold criterion. There is no way to know how this behavior may have influenced and biased results either by inducing anxiety and possibly blood pressure in some subjects. Furthermore, data may have been collected in a potentially more sensitive manner in some subjects and less sensitive manner in some subjects depending on how the health provider interpreted "close" monitoring when the blood pressure approached a threshold criterion.

Considering the many problems that I found with the design and conduct of this study, this inspection report does not provide any positive reassurance that the data that were collected were valid according to the protocol.

CLINICAL REVIEW

10. TABULAR SUMMARY OF KEY PIVOTAL STUDIES

Table 46 summarizes important features of the 3 pivotal efficacy studies.

Table 46 Tabular Summary of Pivotal Efficacy Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)/Other Treatment(s); Dosage Regimen; Route of Administration	No. of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	TVP-1012-232 (TEMPO)	Section 5.3.5.1.1.	Efficacy, tolerability and safety of two doses in PD ⁸ patients not treated with LD ⁷	Multi-center, double-blind, randomized, placebo-controlled/active-controlled, parallel group	Rasagiline mesylate 1, 2 mg oral tablets qd ⁶ administration	404 (266 drug, 138 placebo)	PD ⁸ patients not treated with LD ⁷	52 Weeks (Placebo-controlled for the first 26 weeks and double-blind active phase for the remaining 26 weeks)	Completed: Full
	TVP-1012/232 Sub-Study		Evaluation of the effect of a high oral dose of tyramine in PD ⁸ patients treated with rasagiline mesylate 1 or 2 mg or placebo for 26 weeks		Single dose of tyramine 75 mg on the last dosing day of the 26-week placebo controlled phase	55 (38 drug, 17 placebo)			
Efficacy and Safety	TVP-1012/122 (LARGO)	Section 5.3.5.1.2.	Evaluation of efficacy, tolerability and safety of 1 mg rasagiline mesylate in PD ⁸ subjects with motor fluctuations and LD ⁷ -treated	Multi-center, double-blind, double-dummy, randomized, active and placebo-controlled	Rasagiline mesylate 1 mg oral tablet; qd ⁶ administration/ Entacapone 200 mg oral tablet with each LD ⁷ dose	687 (231 drug, 227 active control, 229 placebo)	PD ⁸ patients treated with LD ⁷	18 Weeks	Completed: Full
Efficacy and Safety	TVP-1012/133 (PRESTO)	Section 5.3.5.1.3.	Evaluation of the efficacy, tolerability, and safety of 0.5 and 1 mg of rasagiline mesylate versus placebo in LD ⁷ -treated PD ⁸ patients with motor fluctuations	Multi-center, double blind, randomized, placebo-controlled, parallel group	Rasagiline mesylate 0.5, 1 mg oral tablets; qd ⁶ administration	472 (313 drug, 159 placebo)	PD ⁸ patients treated with LD ⁷	26 Weeks	Completed: Full
	TVP-1012/133a Sub-Study		Evaluation of the effect of an oral dose of tyramine in PD ⁸ patients treated with rasagiline mesylate versus placebo for 26 weeks		Single tyramine dose of 50 mg, on the last dosing day of 26-weeks	55 (34 drug, 21 placebo)			

11. PIVOTAL STUDIES SHOWING EFFICACY

I focused my efficacy review on individual study reports for the 3 pivotal studies, and respective protocols and amendments. In addition, I reviewed relevant or pertinent sections of summary documents related to efficacy issues.

CLINICAL REVIEW

11.1. Study TVP-1012/232 TEMPO (Study Showing Efficacy)

Description of Protocol TVP-1012/232 TEMPO

Title of Study : TVP-1012/232 (TEMPO) - A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group Clinical Study, for the Efficacy, Tolerability and Safety of Two Doses of Rasagiline Mesylate in Early Parkinson's Disease (PD) Patients Not Treated with Levodopa (LD)

Study initiation date : 11/7/97

Study completion date : 11/29/99 for double-blind placebo-controlled phase and
7/21/00 for active treatment phase

Protocol Description

Objectives :

Primary Objective

The primary objective of this study is to assess the safety and efficacy of rasagiline in PD subjects who are not receiving or requiring carbidopa and levodopa (LD) therapy. The primary efficacy measure will be the change in total UPDRS score, calculated from baseline to 26 weeks, comparing rasagiline 1 mg/day and 2 mg/day with placebo.

Secondary Objectives

The secondary objectives of this study are :

A. Efficacy

- Repeated measures analysis of covariance of the total UPDRS
- Change in individual components of the UPDRS (i.e., mental, motor, and ADL) from baseline to 26 weeks
- Need for levodopa therapy
- Proportion of levodopa-free patients at 26 weeks
- Change in Hoehn & Yah and Schwab and England ADL from baseline to 26 weeks
- Change in timed motor tests from baseline to 26 weeks
- Clinical Global Impression (CGI stratified by center
- Change in Quality of Life (QOL) measurement from baseline to 26 weeks

B. Tolerability: assessed as number of subjects completing the study on their original treatment assignment.

C. Safety will be measured as change in adverse event frequency, changes from baseline in vital signs and clinical laboratory variables.

CLINICAL REVIEW

Double-Blind Placebo-Controlled Phase

STUDY DESIGN and SCHEDULE :

This was a multicenter, double-blind, placebo-controlled, parallel group, Phase III clinical trial for the efficacy, tolerability and safety of two doses of rasagiline mesylate in early Parkinson's disease (PD) subjects not treated with levodopa. Subjects were to be randomized to one of two (1 mg or 2 mg/day) dosages of rasagiline or placebo. Patients were to undergo a 1-week titration phase, followed by a 25-week maintenance phase and a 6-month active treatment extension. A schematic diagram of both phase of the study is shown in Figure 22 .

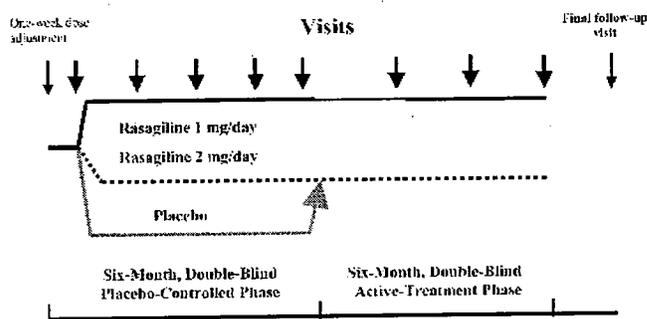
Three hundred and sixty (360) early Parkinson's subjects not treated with levodopa were to be enrolled at approximately 27 North American sites (U.S. and Canada) and were to be equally randomized to 1 of 3 treatment groups (rasagiline 1 or 2 mg/d or placebo). A minimum of 9 subjects was to be enrolled at each site. Prior to any study related procedure as described in this protocol, all subjects were supposed to sign the Investigational Review Board (IRB) approved Informed Consent Form

Assessments

Medical history, vital signs, physical examination, neurological examination (UPDRS). Hoehn and Yah, timed motor tests) and neuropsychological evaluations (MMSE and BDQ and assessment of need for additional anti-parkinsonian therapy were to be evaluated. Assessment of the primary outcome variable ("total" UPDRS = sum of parts I + II + III) and the need for additional anti- parkinsonian therapy were to be performed by the site investigator throughout the study. Need for additional therapy was to be based on four factors: threat to employment, threat to home-making, threat to activities of daily living and threat to ability to manage finances. Criteria for establishing presence of disability requiring additional therapy were to be detailed in the case report forms (CRFs). Other assessments may be performed either by the site investigator or coordinator, but were supposed to be done by the same clinician at each study visit. Study medication compliance was to be checked by counting the study medication that is returned at each visit, and by rasagiline blood levels.

The schedule of activities/assessments for both study phases is shown in Figure 23 .

Figure 22 Schematic Diagram of Study



CLINICAL REVIEW

Figure 23 Schedule of Assessments / Events in Double-Blind Placebo-Controlled Phase and Active Treatment Phase

TEMPO
DOUBLE-BLIND

CONFIDENTIAL

Appendix I: Schedule of Activities

Visit #	FORM #	I - Investigator only								ACTIVE TREATMENT					
		I/C = Both Investigator/Coordinator				X = Investigator				I/C = Both Investigator/Coordinator					
		Screening	Baseline	Week 1	Week 2	Week 14/44	Week 20/20	Week 26	Week 29	Week 32	Week 37	Week 42	Week 52	Final Visit	
		-28 days	0	1	2	3	4	5	51	6	61	7	8	9	
Informed Consent		✓													
Enrollment Projections/Screening Log (SLOG)	L010	✓													
History/Demographic (DEMO)	1100	X													
Inclusion/Exclusion Review ¹ (INEX)	1400	I	I												
Subject Disposition (DISP)	1450		X											X	
Physical Exam (PHYS)	1500	I							I				I	I	
UPDRS (UPDR)	2000	I	I	I	I	I	I	I		I			I	I	
Timed Motor Tests (MOTR)	2100		X	X	X	X	X	X					X	X	
Quality of Life (QOL)	2200		X			X		X					X	X	
Clinical Global Impression (CGI)	2300		X			X		X					X	X	
Beck (BECK)	3000	X	X					X							
Mini Mental (MMSI)	4000	X													
Assess Need for Levodopa (LEVO)	4200		I	I	I	I	I	I	I	I	I	I	I	I	
Vitals (VITL)	6100	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG/Chest X-ray ² (ECG)	6200	I				I		I							
Pharmacokinetics (PHRM)	6300					X		X					X		
AI Level (Metabolite)						X		X					X		
PAI level (drug level)						X		X					X		
Lab Tests ³ (LAB)	6500														
Chemistry Panel		X	X			X		X		X			X	X	
Blood Count, hematology		X	X			X		X		X			X	X	
Urinalysis		X	X			X		X		X			X	X	
Study Termination/Completion: DB (TRM1)	7000													X	
Study Termination/Completion: EXT (TRM2)	7100													X	
Signature Form (SIG)	9000	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	
AE Checklist (AECK)	L100a			X	X	X	X	X	X	X	X	X	X	X	
Adverse Experience Log (AE)	L100			X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Log/PD (MEDP)	L200	X													
Concomitant Medication Checklist (CMCK)	L300a	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Log (CMED)	L300	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Labels (LABL)	L400a		X	X	X	X	X	X	X	X	X	X	X		
Drug Dispensing/Compliance (CMPL)	L400		X	X	X	X	X	X	X	X	X	X	X		
AE Follow-up Log (AEFU)	L500							X					X	X	
¹ Pharmacodynamics Log (DYNM)	L600		X					X					X	X	

¹SAO-B blood samples are drawn on a subset of subjects and sites

²Chest X-ray at screening only

³Serum pregnancy tests at screening, weeks 26 & 52

⁴Review SCR form 1400 at baseline

3/14/98

Inclusion Criteria :

Subjects characterized by all of the following were eligible for participation in the study:

1. Medical Status: Men and women with idiopathic Parkinson's disease (PD) whose diagnosis is confirmed by at least two of the cardinal signs (resting tremor, bradykinesia, rigidity) being present, without other known or suspected cause of parkinsonism.
2. Women must be postmenopausal, surgically-sterilized, or using adequate birth control (e.g. oral contraceptive pills, intra-uterine device, levonorgestrel implant, medroxy progesterone injection). Barrier methods are not adequate. Women of childbearing potential must have a negative pregnancy test (serum beta-HCG test) prior to entry into the study.

CLINICAL REVIEW

3. Subjects must be age 35 years or older.
4. Modified Hoehn and Yah stage < 3.0,
5. Subjects not taking or requiring anti-parkinsonian medications, except for anticholinergics.
 - stable for at least 60 days off of LD, dopamine agonists, and amantadine prior to screening.
 - stable dose of anticholinergics or specified antidepressants (amitriptyline up to a dose of 50 mg a day or trazodone up to a dose of 100 mg a day) for at least 60 days prior to screening and such doses must remain stable throughout the study.
6. Selegiline must be discontinued for at least 90 days prior to screening.
7. Subjects must be withdrawn from selective serotonin reuptake inhibitors (SSRI), other antidepressants (with the exception of amitriptyline and trazodone), meperidine (pethidine) and dextromethorphan for at least 42 days prior to screening.
8. Subjects must be withdrawn from sympathomimetics (including over the counter cold remedies - oral or nasal) for at least 14 days prior to screening.

Exclusion Criteria :

Any of the following were to exclude the subject from participation in the study

1. Subjects with unstable systemic medical problems or clinically significant malignancy, with particular attention to clinically significant or unstable vascular disease (e.g.):
 - clinically significant arrhythmia or valvular heart disease as judged by investigator
 - congestive heart failure (NYHA class G or greater;
 - significant ischemic heart or cerebrovascular disease (such as unstable angina pectoris, stroke or myocardial infarction within the past six months)
 - severe hypertension
 - clinically significant orthostatic hypotension (and/or SBP change >30 mmHg)
 - clinically significant syncope associated with hypotension within the past 2 years
2. Subjects with dementia as defined by MMSE score < 23.
3. Subjects with clinically significant psychiatric illness which compromises their ability to

CLINICAL REVIEW

provide consent or participate fully in the study.

4. Major/severe depression.
5. Subjects who have abnormal clinically significant laboratory test results.
6. Subjects who abuse substances or drugs.
7. Participation in another clinical trial during the previous 60 days or taking any experimental drug within the past 90 days.
8. Subjects with known serious adverse reaction to selegiline (deprenyl).
9. Subjects with known adverse reaction associated with ingestion of tyramine containing food.

Efficacy Variables

Primary

The primary efficacy variable was the change in “total” UPDRS score (sum of parts I + II + III), calculated from baseline to 26 weeks or termination visit, comparing rasagiline 1 mg/day and 2 mg/day with placebo.

Secondary

- Repeated measures analysis of covariance of the total UPDRS
- Change in individual components of the UPDRS (i.e., mental, motor, and ADL) from baseline to 26 weeks
- Need for LD therapy
- Proportion of LD-free patients at 26 weeks
- Change in Hoehn & Yah and Schwab and England ADL from baseline to 26 weeks
- Change in timed motor tests from baseline to 26 weeks
- Clinical Global Impression (CGI stratified by center
- Change in Quality of Life (QOL) measurement from baseline to 26 weeks

Safety and Pharmacokinetic Data were also to be collected. Details regarding the collection and analyses of these outcome measures can be found in the Clinical Safety Review of Dr. Lisa Jones and in the Biopharmaceutical Review of Dr. Andre Jackson.

Discontinuation of Study Therapy

Completed Subjects

A completed study subject is defined as a subject who has met the inclusion criteria of the study and who has successfully completed 52 weeks of therapeutic treatment (26 weeks in the double-

CLINICAL REVIEW

blind followed by 26 weeks of active treatment) or is determined to have reached sufficient disability to require LD/additional therapy under this protocol.

Treatment Discontinuations :

Permanent Discontinuation

Study treatment was to cease, at the discretion of the investigator, if a subject met any study termination criteria as follows:

- Subject with any clinically significant or intolerable adverse event
- Subject refusal to continue treatment for whatever reason
- Investigator's judgment that continued treatments was not in the best interest of the subject
- Pregnancy

Temporary Discontinuation of Study Medication

Study medication could be discontinued if a subject developed an adverse event that was perceived by the investigator to be potentially related to the study material or if the subject was temporarily unable to take study medication for some other reason (e.g. disruption of drug supply, intercurrent illness) If the investigator deemed it appropriate to restart study medication, the subject could resume his/her previously assigned dosage. If either the investigator deemed it inappropriate to restart study medication, or the subject is unwilling to resume the study the subject was to be considered permanently terminated from the study, and was to follow procedures outlined. Subjects undergoing elective surgery with general anesthesia were supposed to discontinue study medication 10 days before surgery if possible and could restart study medication at the time that they were able to resume normal oral dietary intake.

Discontinuation Due to Perceived Need for Additional Anti-Parkinsonian Therapy

Subjects who, in the judgment of the investigator, required additional anti-parkinsonian therapy during the double-blind phase were supposed to be withdrawn from that phase and allowed to begin the active treatment phase. Subjects were supposed to be evaluated before additional anti-parkinsonian therapy is started. Evaluation was supposed to be the same as that performed at visit 5 (week 26 at the end of the double-blind, placebo-controlled phase). Subjects originally on placebo who required additional therapy were to begin the active treatment phase at a dosage of 1 mg of rasagiline per day for one week, and then titrate up to a dose of 2 mg per day. Subjects who had been randomized to 1 or 2 mg rasagiline during the placebo-controlled phase were supposed to receive the same dose of rasagiline during the active treatment phase as received during the double-blind phase of the trial. For subjects in these groups there was to be a sham titration week during which they will receive the same dose of rasagiline that they were taking during the double-blind phase. Subjects still requiring additional therapy after two weeks at a stable dose of rasagiline, were to be seen for an additional unscheduled visit to begin levodopa therapy.

CLINICAL REVIEW

Subjects who, in the judgment of the investigator, developed an urgent need for immediate treatment with carbidopa/LD and could not wait two weeks before starting carbidopa/LD during the double-blind phase of the study were supposed to be started on carbidopa/levodopa in addition to their study medication. Subjects should be seen for an additional, unscheduled visit at the time of starting additional therapy, and every effort should have been made to evaluate these subjects prior to starting additional therapy. The clinical trials coordination center should be contacted as soon as possible in cases of urgent need for carbidopa/LD treatment in order to determine subsequent dosing of study medication.

Treatment During the Active Treatment Period

The active treatment period of the study would begin at week 26 and was to consist of patients who had completed the randomized, double-blinded, placebo-controlled phase or who were required to drop out of the placebo-controlled phase for some reason including the apparent need for additional anti-Parkinson's Disease medical therapy. All subjects would begin treatment with active drug. This treatment was to be conducted under double-blinded conditions. There would be a one week titration for subjects originally assigned to placebo and sham titration for subjects originally assigned to one of the treatment groups. During the titration week, patients originally on either placebo or 1 mg/day of rasagiline would receive 1 mg/day of rasagiline. Patients originally assigned to 2 mg/day of rasagiline were to receive 2 mg/day of rasagiline during this week. After this titration week, all patients were to take the dose to which they had been randomized in the placebo-controlled phase or 2 mg (if they had received placebo in the placebo-controlled phase). The drug supply and labeling was to remain blinded to prevent identification of subjects who had been assigned to placebo in the double-blind phase.

During the active treatment phase, all patients and study personnel would be aware that all patients were being treated with active drug. Patients requiring additional anti-Parkinson's Disease medical therapy would be permitted to remain in the study.

Subjects who, in the judgment of the investigator, required additional therapy during the active treatment phase of the study were to be seen for an additional unscheduled visit to begin therapy either with carbidopa/LD or a marketed dopamine agonist, depending on the clinical preference of the investigator. The dosage of carbidopa/LD or dopamine agonist was also to be at the discretion of the investigator. These subjects were supposed to be evaluated as outlined prior to starting additional therapy. These subjects were not to be considered terminated from the active treatment phase.

Initially, the protocol provided for a follow-up visit 6 weeks (i.e. week 58) after the conclusion of the study at 52 weeks and discontinuation of study treatment, and for various analyses at this timepoint. However, the protocol was subsequently amended to delete the follow-up visit 6 weeks after study treatment discontinuation and to allow patients to enter an open-label, extension trial to collect safety data.

Dose Reduction During Active Treatment Phase

CLINICAL REVIEW

One dose halving was permitted during the active treatment phase of the study. In the event of perceived intolerance, as judged by the investigator, subjects could reduce their dose of study medication by one half. This could be done any time after the first week of the active treatment phase. Dose halving could be accomplished by breaking the tablet in half and taking one half tablet per day rather than one whole tablet. In the event of need for additional anti-parkinsonian therapy, subjects were not supposed to increase their dose of study drug, but rather start treatment with carbidopa/levodopa or dopamine agonist. No dosage reduction was permitted during the double-blind phase.

Planned Analyses / Statistical Methods

Double-Blinded, Placebo-Controlled Phase

Sample Size Rationale

The sole end-point used to assess the sample size required for this trial was the baseline to month six (26 weeks) mean change in "total" UPDRS (i.e. sum of parts I + II + III). Results of power calculations showed that a total of 120 patients enrolled in each of the 3 trial arms would provide adequate power to detect (at 5 % significance level) a real difference between the changes of > 3 "total" UPDRS points.

The power was estimated under the assumption that the pooled standard deviation (SD) of the change from baseline to the last visit of total UPDRS was between 7.40 (estimated from the lazabemide study - *Annals of Neurology* 1996) and 8.75 (estimated from the DATATOP study - PSG internal report). The statistical test used was the t-test comparing the 1 mg group to placebo and the 2 mg group to placebo using Hochberg's Stepup Bonferroni procedure for multiple comparisons, with an overall ("experimentwise") two sided alpha level of 0.05.

For a pooled standard deviation of 7.40 units, the estimated power was calculated to lie between 81% and 93% when the true effect of the 2 mg dose compared to placebo is 3 points and the true effect of the 1 mg dose compared to placebo is between 0 points and 3 points. With a pooled SD of 8.75 units and under the same assumptions as to size of effect, the power was estimated to lie between 66% and 82%.

To examine whether the variance estimate that was used in the above sample size sensitivity analysis was adequate, an assessment of its magnitude was to be performed after 1/3 and 1/2 of the patients will complete 6 months of the double-blind phase. That assessment was to be done without breaking the blind. In the case that the upper bound (because the simple estimate would include the between groups variation) of the variance estimate would be found to be much larger than the one projected, the sponsor reserved the right to increase the study sample size via protocol amendment.

Randomization Procedures

After a patient met the inclusion and exclusion criteria, he/she would be allocated to one of the 3 treatment groups based on a randomization scheme with blocks stratified by centers. The

CLINICAL REVIEW

randomization scheme was to be prepared by the Parkinson Study Group using the SAS random number procedure. The randomization list and the seed used to generate the randomization list was to be kept sealed in a fire protected safe.

Definitions of Datasets For Analysis and Handling of Missing Data

Evaluable Subject: All randomized subjects were to be considered evaluable for tolerability and safety. In accordance with the intent-to-treat (ITT) principle, all subjects randomized were to be kept in their originally assigned treatment group.

Intent-to-treat Cohort (ITT): Consists of all patients who have been randomized.

Completers Cohort (CO): Consists of all patients who completed the 6 months of the double-blind treatment.

Per Protocol Cohort (PP): Consists of all patients who completed the 6 months of the double blind period, did not violate the protocol guidelines, did not miss more than 30% of study drug throughout the study and had at least 80% drug compliance at the last 30 days of the double-blind period .

The Last Observation Carried Forward (LOCF) approach was to be applied to account for early withdrawal and any interim missing data.

Significance Level

The significance level for this study was to be 5% using two-tailed tests. The treatment effect of rasagiline was to be tested for significance by performing two comparisons for each end-point: the group treated with 1 mg/day will be compared to placebo and the group treated with 2 mg/day will also be compared to placebo. Hochberg's stepup Bonferroni method was to be used to maintain the experiment-wise type I error of 5% (two-tailed).

Comparability of Study Groups at Baseline

The 3 treatment groups were to be compared for baseline characteristics in each of the above-mentioned cohorts. This analysis would include demographic data, general medical history, clinical examinations taken prior to trial drug initiation, baseline laboratory data and baseline Parkinson's disease measures including those used for efficacy analyses. The continuous variables were to be examined using the One-way analysis of variance or the Kruskal-Wallis when appropriate and the categorical variables were to be examined for differences between groups using the Chi-Square test or the Fisher's Exact test when appropriate. Descriptive statistics were to be presented by center.

Drop-Out (Drug Tolerability) Assessment

Drug tolerability analysis was to compare the number of subjects who failed to complete the double-blind portion of the study. Time to withdrawal was also to be assessed. Patients who

CLINICAL REVIEW

failed to complete the double-blind period due to LD administration were NOT to be considered as early withdrawals because the time to LD treatment and the proportion of LD-free patients at the end of the double-blind trial period were secondary outcome end-points analyzed for efficacy evaluation.

The comparison was to be performed by applying the CMH test stratified by center. Time to withdrawal was to be presented by Kaplan-Meier curves and was to be compared using the log-rank test.

Efficacy Assessments

Only data collected during the 6 month double-blind period were to be used for assessing the efficacy of rasagiline.

Primary End-Point Analysis

The primary efficacy end-point for this study was the change in “total” UPDRS (i.e. sum of parts I+II+III) from baseline to the six-month visit (week 26). The “total” UPDRS was calculated as the sum of scores of three sub-scales: Mentation (composed of 4 items), ADL (Activities of Daily Living - composed of 13 items, item 16 - tremor, which is composed of 2 items - right and left, was to be averaged) and Motor (composed of 27 items) of the UPDRS. Overall, the “total” UPDRS was composed of 44 items, each item ranged from 0 to 4 points, hence the “total” UPDRS score ranged from 0 to 176 points. A higher UPDRS rating corresponded to worse disease condition. Missing items in the UPDRS scale were to be replaced according to the LOCF rule.

Patients who required LD before the six-month visit and any others who terminated prematurely from the study were to have their last observation carried forward (LOCF).

In the principle/primary analysis, the baseline adjusted analysis of covariance (SAS PROC GLM) was to be used for comparing the adjusted mean differences between the changes observed in each of the active drug groups versus placebo (two comparisons) incorporating terms for treatment and center. The covariates to be included in this model were age, gender, baseline UPDRS, previous use of selegiline and/or anticholinergic agents. The treatment-by-center interaction term was not to be included in the model if it was not statistically significant (i.e. if $p > 0.05$). In case of a significant treatment-by-center interaction data presentation was also to be done on a center by center basis.

Secondary End-Point Analyses

The secondary efficacy end-points analyses for this study were :

- A complementary analysis to the principal analysis was supposed to use repeated measures analysis of covariance (with baseline adjustment incorporating the covariates mentioned in the primary analysis). This additional analysis was to be applied to test differences, among groups, in mean changes from baseline over all visits. Missing values

CLINICAL REVIEW

were to be handled according to the LOCF principle. SAS PROC GLM was to be applied, and was to incorporate treatment and center as factors, while the visit was to serve as the repeated measures factor.

- The individual components of the “total” UPDRS namely, mental, motor and ADL subscales were to be analyzed in the same way as the “total” UPDRS.
- Time to LD Administration: All patients were to be assigned a time. Patients with no reported LD treatment at the end of the 6 months double-blind phase were to be assigned a right-censored value equal to the time that they were in the double-blind phase. The Kaplan-Meier estimates of the distribution of time-to-LD therapy was to be computed for each trial group and the two active groups were to be compared to placebo (two comparisons) using Cox’s proportional hazards model incorporating the above-mentioned list of covariates.
- Proportion of LD-free-patients at the end of the 6-months double-blind phase: This binary end-point was to be summarized in a 2x3 table. LD-free patients who failed to complete the double blind phase were to be categorized, for the purpose of this analysis, with those who required LD treatment. Baseline adjusted logistic regression (incorporating the above list of covariates) were to be performed to compare each of the active groups to placebo (two comparisons).
- Hoehn-Yah staging and the Schwab-England ADL: were to be examined in the same way as the “total” UPDRS.
- Timed Motor Tests were to be analyzed in the same way as the “total” UPDRS.
- Clinical Global Impression (CGI) was to be analyzed using the CMH test stratified by center.
- Quality of life (QOL) parameters were to be analyzed in the same way as the – “total” UPDRS.

Statistical Analyses

SAS software was to be used for statistical analysis and data presentation of the information collected in this study.

Active Treatment Phase

The protocol noted that all patients were to be transferred to an active treatment phase for an additional 6 months at the end of the 6-months of double-blind treatment or at a termination visit for the placebo-controlled phase. The protocol further noted that an exploratory data assessment in the active treatment phase was to attempt to evaluate only the added long-term safety information. However, the sponsor developed a data analysis plan (dated 3/13/01), apparently after the active treatment phase had been completed but

CLINICAL REVIEW

never submitted this Statistical Analysis Plan (SAP) to FDA/DNDP. This SAP outlined the efficacy analyses that were to be conducted for the active treatment phase.

This statistical analysis plan described the following analyses that were to be conducted.

Efficacy Endpoints Analyses

Descriptive statistics and statistical significance tests, were supposed to aim at detecting differences in disease progression, between each of the groups long-term treated with rasagiline (1 mg/day and 2mg/day) and the “placebo-2mg” arm patients. In order to explore the effect of rasagiline as anti-Parkinson monotherapy treatment, efficacy measurements taken after the onset of additional anti-Parkinson's Disease therapy, were not supposed to be included in the statistical analyses, but were to be included in the data listings.

Efficacy measurements that were recorded during the active extension phase, include:

- UPDRS scales
- Need for LD
- Quality of Life (QOL)
- Clinical Global Impression (CGI)
- Timed Motor Tests

It is important to note that the sponsor did not prespecify a single primary analysis of a primary efficacy endpoint for the active treatment phase in the SAP that had been developed but had not been submitted to FDA/DNDP by the sponsor.

UPDRS scales and the Need for Levodopa assessments were both conducted at each one of the active extension visits: week 32, week 42, week 52. The Quality of Life (QOL), Timed Motor Tests and the Clinical Global Impression (CGI) assessments were conducted during the active extension period at week 52. Statistical Analysis of final follow-up visit (Week 58) data will be performed on the FU cohort patients, defined previously.

Primary active treatment efficacy analyses were to include the UPDRS “total” score and the Need for Levodopa assessments.

UPDRS subscales (mentation, ADL, motor), QOL, CGI and Timed motor Tests were considered secondary efficacy variables in the SAP.

Efficacy evaluations were to use the changes from baseline (week 0), at each visit that was conducted before the onset of actual additional anti-PD treatment.

Statistical Tests :

CLINICAL REVIEW

Last Observed Value Carried Forward (LOCF) Analysis

Statistical tests were to use the changes from baseline to termination value (week 52) or last efficacy value before the onset of actual additional therapy (i.e. LOCF), whichever came first. LOCF was also to be used for patients that terminated the active phase before week 52 (and did not begin additional therapy).

Baseline adjusted analysis of covariance was to be used for comparing the adjusted mean differences between the changes observed in each of the active drug groups versus the original placebo (two comparisons) as described for the analyses for the placebo-controlled phase. The statistical model was to include, the effects of treatment and center and the baseline measurement as a covariate. The treatment-by-center interaction term was not to be included in the model if it is not statistically significant (i.e. if $p > 0.05$).

Repeated Measures Analysis

Changes from baseline of total UPDRS, at each active extension phase's visit before the onset of additional therapy, were to be analyzed using a repeated measures model as described for the placebo-controlled phase.

Summary of Significant Protocol Amendments

Amendment No.1 : 3/13/98

- Add a tyramine challenge sub-study to be performed on the last day of treatment in the placebo-controlled phase of the study
- Change of the definition of a secondary end-point: "Need for LD therapy" instead of "LD therapy"
- Eligibility criteria: Shortening of washout period for the following not allowed medications (anti-PD drugs, Some anti-depressant drugs) prior to study entry
- Eligibility criteria: additional medications not allowed in the protocol: St. John Wort
- Allow adjustment of LD or dopamine agonist during the active-treatment phase
- Statistical methods: blinded variance estimate after 1/3 (instead of 1/3 and 1/2) of the patients will complete 26 weeks of the placebo-controlled phase according to the algorithm of Gould and Shi.
- Statistical methods: Description of the method for adjustment for multiple comparisons
- Statistical methods: Addition of complementary analyses : Responders analysis and Repeated measures analysis moved from secondary to complementary analysis and changed to be performed by the SAS MIXED procedure instead of the GLM procedure.

CLINICAL REVIEW

- Deletion of the following sentence from the proportion of patients that did not need LD secondary end-point: “LD-free patients who failed to complete the double blind phase will be categorized, for the purpose of this analysis, with those who required LD treatment.”

Amendment No.2 : 4/22/98

- Canadian sites only- Eligibility criteria: Inclusion of patients with Hoehn & Yah (H&Y) staging < 3.0, while for other study population H&Y staging < 3.0 was allowed.
- Canadian sites only - Eligibility criteria: Washout from LD and dopamine agonists was not allowed expressly for inclusion into the study

Amendment No.3 : 9/1/98

- Eligibility criteria & concomitant therapy: some Selective Serotonin Re-uptake Inhibitors (SSRIs, i.e. sertraline, paroxetine and fluvoxamine maleate) were allowed, at stable low doses, during the study
- Concomitant therapy: allow the use of a greater variety of anti-PD medications (but not dopaminergic medical treatments) when additional therapy is deemed necessary in the active-treatment phase

Amendment No.4 : 11/13/98

- Week 58 visit, 6 weeks after study completion, is to be omitted for patient continuing immediately into the open-label extension protocol: TVP-1012/233
- Concomitant therapy: limit the use of the allowed SSRIs (i.e. sertraline, paroxetine and fluvoxamine maleate) to the active-treatment phase only (change to amendment 3)

Amendment No 5. : 11/1/99

- Change in the definition of “Responder Analysis”. It was primarily intended to evaluate the proportion of patients with a 30% improvement in Total UPDRS. The revised analysis would be: The total UPDRS change from baseline to the six-month visit, will be dichotomized according to the cut-off point of 3 UPDRS points. Non-responders will be defined as patients with a 3 or more points worsening in total UPDRS. All other patient will be considered responders.
- Provide at-home blood pressure monitoring around meal for those patients taking additional anti-Parkinsonian medication (LD or dopamine agonists) in comparison to rasagiline alone

Amendment No 6. : 1/31/00

CLINICAL REVIEW

- Restrict the intake of foods high in tyramine content for patients treated concomitantly with LD that were already in their active-treatment phase.
- Restrict the at-home blood pressure monitoring to patients receiving rasagiline and LD (change to amendment 5). Patients receiving rasagiline and LD who do not agree to participate in the at-home blood pressure monitoring sub-study would be re-supplied with blinded test drug consisting of rasagiline, 1 mg, even if they maintain a tyramine-restricted diet

Amendment No 7. : 7/10/00

- A letter was sent to the study sites on March 2000 in which all patients were required to initiate a tyramine-restricted diet. It was applicable for only 28 (out of 380) patients that were still treated in the active-treatment phase of the study. By the time that the formal amendment was issued, dosing had already been completed for all TEMPO patients.
 - New data from the tyramine challenge sub-study performed in 55 patients who completed the placebo-controlled phase of TEMPO (TVP-1012/232) was added. These patients demonstrated mild, asymptomatic and transient elevations in blood pressure in two patients treated with 2 mg/day rasagiline, consistent with a potential interaction between tyramine and rasagiline, even in the absence of LD therapy although not meeting the criteria for tyramine reaction as defined in the protocol.

11.1.1. Sponsor's Presentation of Results of TVP-1012/232 TEMPO

Most of the descriptions, summaries, tables, and figures presented here were taken from the sponsor's electronic submission.

Patient Disposition

Four hundred and seventy-three (473) patients were screened. Of these, 404 (84%) patients enrolled into this study in USA (28 centers) and in Canada (4 centers) and were randomly allocated to three treatment groups: 1 or 2 mg rasagiline or placebo (Table 47).

Table 47 Distribution of Patients by Country

TVP-1012/232 Placebo-Controlled Phase	1 mg		2 mg		PLACEBO		All	
	N	%	N	%	N	%	N	%
CANADA	18	13.4	14	10.6	15	10.9	47	11.6
USA	116	86.6	118	89.4	123	89.1	357	88.4
All	134	100.0	132	100.0	138	100.0	404	100.0

Table 48 summarizes the termination reasons by treatment group and the need for additional/LD therapy. One hundred and eleven (82.8%) patients on 1 mg rasagiline, 105 (79.5%) patients on 2 mg rasagiline and 112 (81.2%) patients on placebo completed the 6-month, placebo-

CLINICAL REVIEW

controlled phase of the study without needing LD therapy. Patients, who failed to complete the placebo-controlled phase due to a need for LD and continued into the active-treatment phase, were not considered as early or premature withdrawals. Patients were not considered to have discontinued prematurely from the study if they left the randomized, double-blind, placebo-controlled phase because of a need for additional anti-Parkinson's Disease therapy. Patients who left the double-blinded, placebo-controlled phase because of a need for additional Parkinson's Disease medical therapy and then entered the active treatment phase were considered to have exhibited "normal completion" as did patients who did not require additional Parkinson's Disease medical therapy and who completed the 6 months of the placebo-controlled phase. Termination reasons dichotomized by the need for additional/LD therapy are presented in Table 48. A "total" of 22 (5.4%) patients did not complete the initial 26 weeks of the study. Nine (6.7%), 8 (6.1%) and 5 (3.6%) patients on 1, 2 mg rasagiline and placebo, respectively, did not have a normal conclusion. The differences between treatment groups in the number of patients with premature termination or the time on study to termination were not statistically significant.

Protocol Violations

The incidence of major protocol violations is shown in Table 49.

Table 48 Summary of Termination Reasons Categorized By Presence and Absence of a Need for Additional* anti-Parkinson's Disease Therapy

TVP-1012/232 Placebo-Controlled Phase		1 mg		2 mg		PLACEBO		All	
		N	%	N	%	N	%	N	%
Need for Additional Therapy	Termination Reason								
	No								
	Normal Completion	111	93.3	105	95.5	112	97.4	328	95.3
	Adverse Experience	5	4.2	1	0.9	1	0.9	7	2.0
	Failed to Return	1	0.8	1	0.3
	Subject Request	2	1.7	2	1.8	2	1.7	6	1.7
	Unsatisfactory Response	.	.	1	0.9	.	.	1	0.3
	Other	.	.	1	0.9	.	.	1	0.3
All	119	88.8	110	83.3	115	83.3	344	85.1	
Yes	Termination Reason								
	Normal Completion	14	93.3	19	86.4	21	91.3	54	90.0
	Adverse Experience	.	.	1	4.5	.	.	1	1.7
	Subject Request	1	4.3	1	1.7
	Unsatisfactory Response	.	.	1	4.5	1	4.3	2	3.3
	Protocol Violation	.	.	1	4.5	.	.	1	1.7
	Other	1	6.7	1	1.7
	All	15	11.2	22	16.7	23	16.7	60	14.9
All	Termination Reason								
	Normal Completion	125	93.3	124	93.9	133	96.4	382	94.6
	AE	5	3.7	2	1.5	1	0.7	8	2.0
	Failed to Return	1	0.7	1	0.2
	Subject Request	2	1.5	2	1.5	3	2.2	7	1.7
	Unsatisfactory Response	.	.	2	1.5	1	0.7	3	0.7
	Protocol Violation	.	.	1	0.8	.	.	1	0.2
	Other	1	0.7	1	0.8	.	.	2	0.5
All	134	100.0	132	100.0	138	100.0	404	100.0	

*assessed as a need for LD

CLINICAL REVIEW

Table 49 Incidence of Protocol Violations

TVP-1012/232 Placebo-Controlled Phase	1 mg (N=134)		2 mg (N=132)		PLACEBO (N=138)		All (N=404)	
	N	%	N	%	N	%	N	%
Protocol Violation								
Overall Compliance <70%	0	0.0	1	0.8	0	0.0	1	0.2
Last Month Compliance <80%	0	0.0	3	2.3	2	1.4	5	1.2
Washout Period from Selegiline	0	0.0	0	0.0	2	1.4	2	0.5
St John Wort	0	0.0	0	0.0	2	1.4	2	0.5
Early Termination	9	6.7	8	6.1	5	3.6	22	5.4
Anticholinergic Dose Change	2	1.5	2	1.5	0	0.0	4	1.0
Informed Consent	3	2.2	3	2.3	1	0.7	7	1.7
All	13	9.7	14	10.6	11	8.0	38	9.4

Demographic Characterizations

Summary statistics of baseline demographic characteristics are provided in Table 50. All baseline results obtained during the placebo-controlled phase of the study were statistically tested for significance level. As demonstrated, patients did not differ significantly by treatment group in terms of age (61 years, range 32-92) or sex. Most (~ 95%) of the patients were Caucasians. The 3 treatment groups were also comparable with respect to drug abuse, alcohol consumption and smoking.

Table 50 Demographic Characteristics

TVP-1012/232 Placebo-Controlled Phase			1 mg	2 mg	PLACEBO	All
Height (cm)	All	N	134	132	138	404
		Mean	171.6	171.6	171.9	171.7
		Std	9.0	9.7	9.7	9.4
		Min	149.9	149.9	147.5	147.5
		Max	192.0	190.0	191.1	192.0
	Male	N	90	74	93	257
		Mean	176.2	178.1	176.7	176.9
		Std	6.2	6.9	7.3	6.9
		Min	165.0	155.0	154.2	154.2
		Max	192.0	190.0	191.1	192.0
	Female	N	44	58	45	147
		Mean	162.1	163.3	162.0	162.5
		Std	5.7	5.4	5.7	5.6
		Min	149.9	149.9	147.5	147.5
		Max	172.7	175.3	175.0	175.3
Weight (kg)	All	N	134	132	138	404
		Mean	77.6	80.7	76.8	78.3
		Std	14.0	14.9	14.8	14.6
		Min	46.4	50.9	45.9	45.9
		Max	121.4	140.0	131.8	140.0
	Male	N	90	74	93	257
		Mean	82.6	86.8	82.6	83.8
		Std	11.9	12.0	12.8	12.4
		Min	63.6	58.2	54.5	54.5
		Max	121.4	117.3	131.8	131.8
	Female	N	44	58	45	147
		Mean	67.2	72.9	65.0	68.8
		Std	12.2	14.7	11.3	13.4
		Min	46.4	50.9	45.9	45.9
		Max	95.5	140.0	93.1	140.0
Age (years)	N	134	132	138	404	
	Mean	61.6	60.4	60.5	60.8	
	Std	10.3	11.4	10.8	10.8	
	Min	33.0	32.0	38.0	32.0	
	Max	92.0	79.0	79.0	92.0	

Parkinson's Disease Characteristics

CLINICAL REVIEW

Diagnosis

Symptoms at the time of PD diagnosis for all patients are presented in Table 51 by treatment group. Most patients had defined symptoms and signs of the disease such as tremor, rigidity and bradykinesia. Less than one sixth of the patients exhibited postural disturbances at the time of diagnosis. No statistically significant differences were observed between the groups (Chi-square test). The sponsor noted that these characteristics are comparable with those reported for early PD patients, and thus the patients studied represent the general targeted patient population.

Table 51 Parkinson's Disease Symptoms at Time of Diagnosis

TVP-1012/232 Placebo-Controlled Phase	1 mg		2 mg		PLACEBO		All	
	N	%	N	%	N	%	N	%
Tremor								
Yes	114	85.1	116	87.9	111	80.4	341	84.4
No	20	14.9	16	12.1	27	19.6	63	15.6
All	134	100.0	132	100.0	138	100.0	404	100.0
Rigidity								
Yes	86	64.2	96	72.7	91	65.9	273	67.6
No	44	32.8	35	26.5	46	33.3	125	30.9
Unknown	4	3.0	1	0.8	1	0.7	6	1.5
All	134	100.0	132	100.0	138	100.0	404	100.0
Bradykinesia								
Yes	82	61.2	85	64.4	102	73.9	269	66.6
No	48	35.8	44	33.3	33	23.9	125	30.9
Unknown	4	3.0	3	2.3	3	2.2	10	2.5
All	134	100.0	132	100.0	138	100.0	404	100.0
Posture								
Yes	15	11.2	20	15.2	18	13.0	53	13.1
No	115	85.8	110	83.3	118	85.5	343	84.9
Unknown	4	3.0	2	1.5	2	1.4	8	2.0
All	134	100.0	132	100.0	138	100.0	404	100.0
Other								
N	17	12.7	25	18.9	25	18.1	67	16.6
Yes	32	23.9	30	22.7	35	25.4	97	24.0
No	78	58.2	75	56.8	72	52.2	225	55.7
Unknown	7	5.2	2	1.5	6	4.3	15	3.7
All	134	100.0	132	100.0	138	100.0	404	100.0

Disease Duration and Baseline Characteristics

On average, mean disease duration in all treatment groups was one year at study entry : 0.94 year for the placebo, 0.93 year for the 1 mg rasagiline and 1.16 year for the 2 mg group (ranged from few days to 10.6 years). Disease duration for all treatment groups was similar (ANOVA).

Baseline disease characteristics are displayed in Table 52 . Most baseline disease parameters assessed were considered comparable between treatment groups. There were no statistical significant differences (ANOVA) among the treatment groups, with the exception of UPDRS mental scale ($p = 0.0123$) and of Severity of Illness scale (mean Severity of Illness 1.66 – 1 mg; 1.83 – 2 mg; 1.65 – placebo) for which there was a borderline significant difference ($p = 0.0508$).

CLINICAL REVIEW

Table 52 Baseline Disease Characteristics

TVP-1012/232 Placebo-controlled Phase		1 mg	2 mg	PLACEBO	All
Total UPDRS	N	134	132	138	404
	Mean	24.69	25.89	24.54	25.03
	Std	11.25	9.54	11.61	10.84
	Min	5.50	10.50	5.50	5.50
	Max	75.00	53.50	61.00	75.00
UPDRS Mental 1-4	N	134	132	138	404
	Mean	0.94	1.20	0.79	0.98
	Std	1.11	1.27	1.08	1.16
	Min	0.00	0.00	0.00	0.00
	Max	4.00	6.00	5.00	6.00
UPDRS ADL 5-17	N	134	132	138	404
	Mean	5.90	6.73	6.16	6.26
	Std	3.35	3.22	3.53	3.38
	Min	0.50	0.50	0.50	0.50
	Max	17.00	19.50	20.00	20.00
UPDRS Motor 18-44	N	134	132	138	404
	Mean	17.85	17.95	17.59	17.80
	Std	8.89	7.52	8.84	8.43
	Min	4.00	4.00	3.00	3.00
	Max	58.50	36.50	46.00	58.50
S/E ADL Subject	N	134	132	138	404
	Mean	92.31	90.68	91.81	91.61
	Std	5.87	7.04	5.95	6.32
	Min	70.00	50.00	70.00	50.00
	Max	100.00	100.00	100.00	100.00
S/E ADL Rater	N	134	132	138	404
	Mean	92.16	90.23	91.20	91.20
	Std	5.67	6.17	6.32	6.10
	Min	70.00	70.00	70.00	70.00
	Max	100.00	100.00	100.00	100.00

TVP-1012/232 Placebo-controlled Phase		1 mg	2 mg	PLACEBO	All
H/Y Stage	N	134	132	138	404
	Mean	1.85	1.88	1.86	1.86
	Std	0.48	0.48	0.50	0.48
	Min	1.00	1.00	1.00	1.00
	Max	3.00	3.00	3.00	3.00
QOL Score	N	134	132	138	404
	Mean	28.30	30.19	26.95	28.46
	Std	15.16	16.79	15.67	15.90
	Min	4.00	3.00	1.00	1.00
	Max	75.00	88.00	70.00	88.00
Timed Motor Test Score (sec)	N	134	131	137	402
	Mean	12.78	13.02	13.52	13.11
	Std	3.91	3.25	6.24	4.67
	Min	6.83	6.67	6.00	6.00
	Max	31.33	25.67	62.17	62.17
BECK Total Score	N	134	132	138	404
	Mean	2.39	3.05	2.54	2.66
	Std	2.47	3.22	2.79	2.85
	Min	0.00	0.00	0.00	0.00
	Max	12.00	20.00	16.00	20.00
Mini Mental Status	N	134	132	138	404
	Mean	29.1	29.1	29.2	29.1
	Std	1.5	1.3	1.2	1.3
	Max	24.0	25.0	25.0	24.0
	Min	30.0	30.0	30.0	30.0
Mean	29.1	29.1	29.2	29.1	

Medical History

Patients in all treatment groups had a medical history of a variety of additional illnesses (current or past), that were not considered to interfere with study treatment.

Previous and Concomitant Medications

CLINICAL REVIEW

It appeared that the most commonly used medications prior to study entry were similar to those consumed during the treatment period except for dopaminergic agents that were taken by one third of the patients prior to study entry and were not allowed during the placebo-controlled phase. There was no noteworthy differences in the specific type of dopaminergic therapy (e.g. LD or specific dopaminergic agonist) used prior to study enrollment among the 3 treatment groups:

Almost all patients consumed concomitant medications (Table 53). No differences were found between treatment groups in the overall incidence of medication consumption. The most commonly used medications were analgesics and anti-inflammatory agents, cardiovascular agents and gastrointestinal agents. Nutritional agents and vitamins were also frequently used. No patients received LD between the placebo-controlled phase and the active treatment phase due to an urgent need for LD.

Table 53 Concomitant Medications

1VP-1012/232 Placebo-Controlled Phase	1 mg (N=134)		2 mg (N=132)		PLACEBO (N=138)	
	N	%	N	%	N	%
- ALL	129	96.3	127	96.2	135	97.8
ANAESTHETICS-UNSPECIFIED	3	2.2	2	1.5	2	1.4
ANALGESICS AND ANTI-INFLAMMATORY AGENTS	89	66.4	95	72.0	95	68.8
ANTIBACTERIAL AGENTS	26	19.4	30	22.7	22	15.9
ANTIDEPRESSANTS	16	11.9	14	10.6	13	9.4
ANTI-DIABETIC AGENTS	8	6.0	5	3.8	4	2.9
ANTI-EPILEPTICS	3	2.2	2	1.5	5	3.6
ANTI-FUNGAL AGENTS	5	3.7	1	0.8	7	5.1
ANTI-GOUT AGENTS	2	1.5	2	1.5	3	2.2
ANTIMALARIALS	1	0.7	2	1.5	1	0.7
ANTI-MIGRAINE AGENTS	2	1.4
ANTIMUSCARINIC AGENTS	12	9.0	14	10.6	21	15.2
ANTI-NEOPLASTIC & IMMUNOSUPPRESSANTS	1	0.7	2	1.5	.	.
ANTI-PROTOZOAL AGENTS	2	1.5	4	3.0	.	.
ANTIVIRAL AGENTS	1	0.7	.	.	1	0.7
ANXIOLYTIC, SEDATIVE, HYPNOTIC, NEUROLEPTIC	22	16.4	11	8.3	11	8.0
BLOOD PRODUCTS, PLASMA EXPANDERS & HEMOSTA	1	0.7	1	0.8	.	.
BONE MODULATING DRUGS	2	1.5	4	3.0	6	4.3
BRONCHODILATORS AND ANTI-ASTHMA DRUGS	12	9.0	5	3.8	10	7.2
CARDIOVASCULAR AGENTS	56	41.8	51	38.6	56	40.6
CHELATING AGENTS, ANTIDOTES, ANTAGONISTS	1	0.7
CORTICOSTEROIDS	17	12.7	14	10.6	23	16.7
COUGH SUPPRESSANTS & MUCOLYTICS	12	9.0	7	5.3	11	8.0
DERMATOLOGICAL AGENTS	1	0.7	3	2.3	1	0.7
DISINFECTANTS AND PRESERVATIVES	1	0.7	.	.	2	1.4
DOPAMINERGIC AGENTS	1	0.7	.	.	1	0.7
ELECTROLYTES	20	14.9	28	21.2	28	20.3
GASTROINTESTINAL AGENTS	42	31.3	39	29.5	42	30.4
GENERAL ANAESTHETICS	2	1.5
HERBAL	11	8.2	13	9.8	12	8.7
HISTAMINE H1 RECEPTOR ANTAGONISTS	27	20.1	25	18.9	25	18.1
HYPOTHALAMIC AND PITUITARY HORMONES	1	0.7	2	1.5	.	.
LIPID REGULATING AGENTS	17	12.7	17	12.9	16	11.6
LOCAL ANAESTHETICS	7	5.2	8	6.1	8	5.8
MUSCLE RELAXANTS	7	5.2	2	1.5	.	.
NUTRITIONAL AGENTS AND VITAMINS	75	56.0	74	56.1	86	62.3
PARAFFINS AND SIMILAR BASES	1	0.7
PARASYMPATHOMIMETICS	2	1.5	1	0.8	2	1.4
PROSTAGLANDINS	5	3.7	1	0.8	4	2.9
SEX HORMONES	22	16.4	33	25.0	22	15.9
SOAPS AND OTHER ANIONIC SURFACTANTS	.	.	1	0.8	.	.
STABILISING AND SUSPENDING AGENTS	4	3.0	3	2.3	3	2.2
SUNSCREENS	1	0.7
SUPPLEMENTARY DRUGS & OTHER SUBSTANCES	27	20.1	26	19.7	36	26.1
THYROID AND ANTITHYROID AGENTS	13	9.7	12	9.1	9	6.5
VACCINES, IMMUNOGLOBULINS AND ANTISERA	7	5.2	5	3.8	6	4.3

Treatment Compliance

CLINICAL REVIEW

Study drug compliance was estimated by regular drug intake, containers dispensed, number of used returned containers and number of days since last visit. The calculated compliance rates were similar (~ 99 %) in all treatment groups.

Efficacy Results

All efficacy results obtained during the placebo-controlled phase of the study were statistically tested for significance level.

“Total” UPDRS Score and Change from Baseline

The sponsor noted that it evaluated “total” UPDRS scores but actually evaluated the sum of scores for parts I, II, and III (i.e. mental, ADL, and motor subscales) for the calculation of “total” UPDRS. “Total” UPDRS and the change from baseline are shown by visit in Table 54. The LOCF imputation scheme was implemented to account for early discontinuation and any interim missing data.

A small decrease from baseline in “total” UPDRS was measured in all treatment groups at Week 4 in study, which disappeared in the next visit in the placebo group. Thereafter, “total” UPDRS score was sustained for 16 weeks in actively treated patients and increased steadily (representing worsening of the disease) in placebo patients. Overall, following 26-week treatment period, the mean “total” UPDRS score remained similar to baseline in patients treated with rasagiline. An increase of approximately 16 % (4 points) in the mean “total” UPDRS score was calculated for placebo patients (Table 54).

The assessment of the data as observed (Actual Visit) was also performed to rule out any possible source of bias in the results and conclusions that was attributed to early withdrawals or any interim missing observations. As demonstrated in Table 55, the results obtained using the Actual Visit imputations were similar to those calculated using LOCF (Table 55).

Sponsor’s Primary Efficacy Endpoint

Primary End-Point . Change in “Total” UPDRS from Baseline to Week 26

The principal statistical analysis compared the mean change from baseline in “total” UPDRS for each of the active-treatment groups to placebo (two contrasts) using ANCOVA adjusted for baseline UPDRS, treatment, center and treatment-by-center interaction. The mean “total” UPDRS scores at baseline for all randomized patients were similar across all treatment groups. Following 26 weeks of treatment, the change from baseline UPDRS differed significantly between either of the active-treatment group and the placebo ($p < 0.0001$ for both contrasts using Hochberg’s Step-up Bonferroni procedure for multiple comparisons). The adjusted mean change from baseline in “total” UPDRS score was -0.13 (95% CI:[-1.16, 0.91]) for the 1 mg group and 0.51 (95% CI:[-0.55, 1.57]) for the 2 mg group. Patients receiving

CLINICAL REVIEW

Table 54 Descriptive Statistics of “Total” UPDRS and Change from baseline by Visit using the LOCF Imputation Scheme

TVP-1012/232 Placebo-Controlled Phase		Total UPDRS				Total UPDRS (Change from Baseline)			
		1 mg	2 mg	PLACEBO	All	1 mg	2 mg	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	24.69	25.89	24.54	25.03	0.00	0.00	0.00	0.00
	Std	11.25	9.54	11.61	10.84	0.00	0.00	0.00	0.00
	Min	5.50	10.50	5.50	5.50	0.00	0.00	0.00	0.00
	Max	75.00	53.50	61.00	75.00	0.00	0.00	0.00	0.00
Week 4	N	134	132	138	404	134	132	138	404
	Mean	23.68	24.47	24.29	24.15	-1.01	-1.41	-0.24	-0.88
	Std	11.59	10.31	12.14	11.36	4.57	4.34	5.47	4.84
	Min	3.50	3.50	5.50	3.50	-15.00	-11.50	-17.50	-17.50
	Max	75.50	53.00	83.00	83.00	11.00	9.50	22.00	22.00
Week 8	N	134	132	138	404	134	132	138	404
	Mean	23.18	24.63	25.65	24.50	-1.51	-1.25	1.12	-0.53
	Std	11.50	11.01	13.39	12.04	5.24	5.17	6.34	5.73
	Min	3.50	3.50	5.00	3.50	-31.00	-18.00	-12.50	-31.00
	Max	62.50	61.00	83.00	83.00	11.50	14.00	25.50	25.50
Week 14	N	134	132	138	404	134	132	138	404
	Mean	23.32	24.99	26.01	24.79	-1.37	-0.89	1.48	-0.24
	Std	11.31	10.98	13.59	12.06	5.75	5.35	6.49	6.01
	Min	3.50	1.00	5.00	1.00	-27.50	-11.50	-14.50	-27.50
	Max	61.50	56.00	83.00	83.00	12.00	12.00	22.00	22.00
Week 20	N	134	132	138	404	134	132	138	404
	Mean	24.04	25.64	27.28	25.67	-0.65	-0.24	2.75	0.64
	Std	12.27	11.49	14.05	12.70	6.32	5.81	6.99	6.56
	Min	3.50	3.00	6.50	3.00	-37.00	-14.50	-19.00	-37.00
	Max	75.00	58.00	83.00	83.00	15.00	16.00	24.00	24.00
Week 26/Termination	N	134	132	138	404	134	132	138	404
	Mean	24.75	26.61	28.44	26.62	0.06	0.72	3.91	1.59
	Std	12.26	11.83	14.30	12.92	6.82	5.82	7.45	6.93
	Min	4.00	3.50	5.00	3.50	-39.00	-14.00	-18.50	-39.00
	Max	60.00	58.00	83.00	83.00	26.00	21.00	23.50	26.00

Table 55 Descriptive Statistics of “Total” UPDRS and Change from baseline by Visit using the Actual Visit Imputation Scheme

TVP-1012/232 Placebo-Controlled Phase		Total UPDRS				Total UPDRS (Change from Baseline)			
		1 mg	2 mg	PLACEBO	All	1 mg	2 mg	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	24.69	25.89	24.54	25.03	0.00	0.00	0.00	0.00
	Std	11.25	9.54	11.61	10.84	0.00	0.00	0.00	0.00
	Min	5.50	10.50	5.50	5.50	0.00	0.00	0.00	0.00
	Max	75.00	53.50	61.00	75.00	0.00	0.00	0.00	0.00
Week 4	N	134	132	137	403	134	132	137	403
	Mean	23.68	24.47	24.41	24.19	-1.01	-1.41	-0.24	-0.88
	Std	11.59	10.31	12.11	11.35	4.57	4.34	5.49	4.85
	Min	3.50	3.50	5.50	3.50	-15.00	-11.50	-17.50	-17.50
	Max	75.50	53.00	83.00	83.00	11.00	9.50	22.00	22.00
Week 8	N	128	127	136	391	128	127	136	391
	Mean	22.96	24.13	25.09	24.08	-1.59	-1.49	0.96	-0.67
	Std	11.62	10.74	12.44	11.64	5.31	5.01	6.13	5.63
	Min	3.50	3.50	5.00	3.50	-31.00	-18.00	-12.50	-31.00
	Max	62.50	61.00	70.00	70.00	11.50	14.00	25.50	25.50
Week 14	N	125	122	135	382	125	122	135	382
	Mean	22.99	24.07	25.39	24.18	-1.56	-1.30	1.26	-0.48
	Std	11.40	10.49	12.69	11.61	5.77	5.08	6.26	5.87
	Min	3.50	1.00	5.00	1.00	-27.50	-11.50	-14.50	-27.50
	Max	61.50	56.00	64.50	64.50	12.00	12.00	21.00	21.00
Week 20	N	118	117	120	355	118	117	120	355
	Mean	23.46	24.41	25.20	24.36	-0.85	-0.76	1.93	0.12
	Std	12.11	11.05	12.01	11.72	6.45	5.53	6.67	6.36
	Min	3.50	3.00	6.50	3.00	-37.00	-14.50	-19.00	-37.00
	Max	75.00	58.00	66.50	75.00	15.00	16.00	24.00	24.00
Week 26/Termination	N	115	107	115	337	115	107	115	337
	Mean	24.09	24.57	26.24	24.97	-0.00	-0.05	3.31	1.11
	Std	12.21	11.52	12.71	12.17	7.09	5.56	7.44	6.93
	Min	4.00	3.50	5.00	3.50	-39.00	-14.00	-18.50	-39.00
	Max	60.00	58.00	65.00	65.00	26.00	21.00	23.50	26.00

placebo showed an increase of 4.07 (95% CI:[3.04, 5.10]) points. Thus, the treatment effect (i.e. active treatment – placebo) exerted by 1 and 2 mg rasagiline was -4.20 (95% CI:[-5.66,-2.73]) and -3.56 (95% CI:[-5.04,-2.08]), respectively.

CLINICAL REVIEW

Hypothesis Testing

In addition to the original, pre-defined principal analysis of the primary end-point, multiple statistical models were fitted to the primary end-point data in order to demonstrate the robustness of the results and conclusions. Most of these showed nominally statistically significant p values. As shown in Figure 24, the mean treatment effects for most of the centers are consistent. Inconsistent mean treatment effect discovered in few centers may be attributable to relatively small sample size in some of these centers (centers #8, 40 and 60 enrolled only 8, 7 and 9 patients, respectively).

Figure 24 Mean Treatment Effect by Center

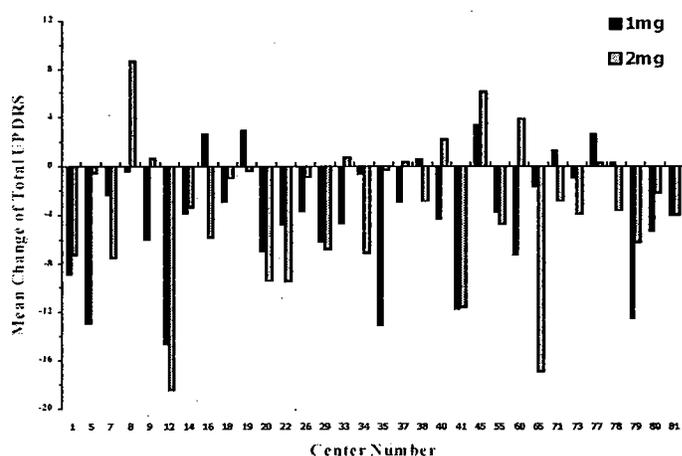


Table 56 demonstrates the distribution of randomized patients by treatment group and cohort (i.e. ITT, completer, per protocol).

Table 56 Distribution of Cohorts

TVP-1012/232 Placebo-Controlled Phase	1 mg		2 mg		PLACEBO		All	
	N	%	N	%	N	%	N	%
Total Enrolled	134	100.0	132	100.0	138	100.0	404	100.0
ITT Cohort								
Yes	134	100.0	132	100.0	138	100.0	404	100.0
CO Cohort								
No	9	6.7	8	6.1	5	3.6	22	100.0
Yes	125	93.3	124	93.9	133	96.4	382	100.0
PP Cohort								
No	11	8.2	11	8.3	10	7.2	32	100.0
Yes	123	91.8	121	91.7	128	92.8	372	100.0

A consistent and robust drug treatment effect was demonstrated for all three patient cohorts (Figure 25). Table 57 shows the mean change in “total” UPDRS from baseline for the different treatment groups for the 3 cohorts and Figure 25 shows the treatment effect. Because the drop-out rate was also comparable between groups (Table 48), all other end-points were analyzed for the ITT cohort only.

CLINICAL REVIEW

Table 57 Descriptive Statistics of “Total” UPDRS and Change from Baseline by Patient Cohort (ITT, Completer, Per Protocol)

ITT Cohort

TVP-1012/232 Placebo-Controlled Phase		1 mg	2 mg	PLACEBO	All
Total UPDRS (Baseline)	N	134	132	138	404
	Mean	24.69	25.89	24.54	25.03
	Std	11.25	9.54	11.61	10.84
	Min	5.50	10.50	5.50	5.50
	Max	75.00	53.50	61.00	75.00
Total UPDRS (Termination)	N	134	132	138	404
	Mean	24.75	26.61	28.44	26.62
	Std	12.26	11.83	14.30	12.92
	Min	4.00	3.50	5.00	3.50
	Max	60.00	58.00	83.00	83.00
Total UPDRS (Change)	N	134	132	138	404
	Mean	0.06	0.72	3.91	1.59
	Std	6.82	5.82	7.45	6.93
	Min	-39.00	-14.00	-18.50	-39.00
	Max	26.00	21.00	23.50	26.00

Completers Cohort

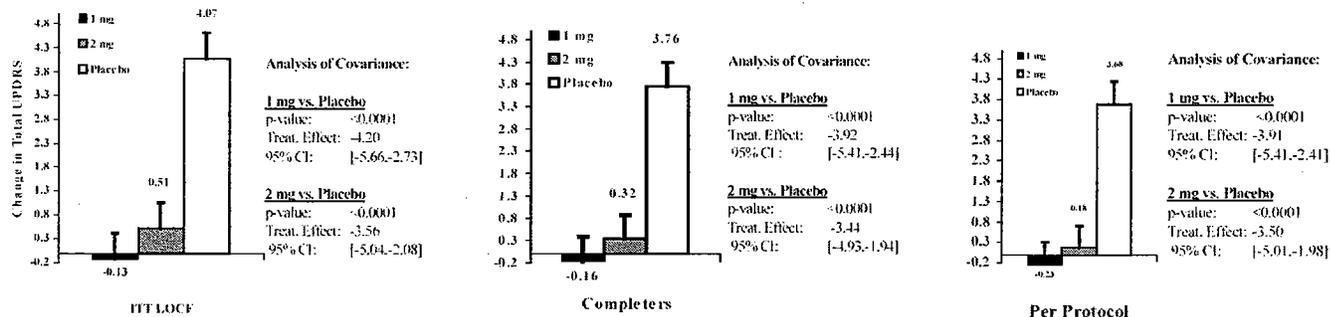
TVP-1012/232 Placebo-Controlled Phase		1 mg	2 mg	PLACEBO	All
Total UPDRS (Baseline)	N	125	124	133	382
	Mean	24.43	25.44	23.76	24.53
	Std	11.47	9.54	10.84	10.65
	Min	5.50	10.50	5.50	5.50
	Max	75.00	53.50	57.00	75.00
Total UPDRS (Termination)	N	125	124	133	382
	Mean	24.34	26.00	27.53	25.99
	Std	12.28	11.80	13.35	12.55
	Min	4.00	3.50	5.00	3.50
	Max	60.00	58.00	65.00	65.00
Total UPDRS (Change)	N	125	124	133	382
	Mean	-0.09	0.56	3.77	1.46
	Std	6.62	5.78	7.39	6.85
	Min	-39.00	-14.00	-18.50	-39.00
	Max	13.50	21.00	23.50	23.50

Per Protocol Cohort

TVP-1012/232 Placebo-Controlled Phase		1 mg	2 mg	PLACEBO	All
Total UPDRS (Baseline)	N	123	121	128	372
	Mean	24.36	25.31	23.68	24.43
	Std	11.54	9.41	11.03	10.70
	Min	5.50	10.50	5.50	5.50
	Max	75.00	53.50	57.00	75.00
Total UPDRS (Termination)	N	123	121	128	372
	Mean	24.27	25.78	27.41	25.84
	Std	12.34	11.68	13.46	12.56
	Min	4.00	3.50	5.00	3.50
	Max	60.00	58.00	65.00	65.00
Total UPDRS (Change)	N	123	121	128	372
	Mean	-0.09	0.47	3.74	1.41
	Std	6.66	5.82	7.32	6.84
	Min	-39.00	-14.00	-18.50	-39.00
	Max	13.50	21.00	23.50	23.50

CLINICAL REVIEW

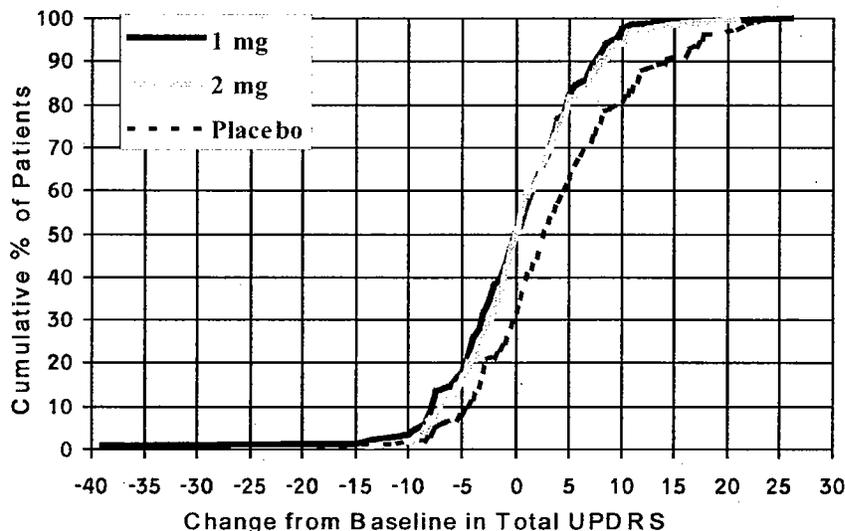
Figure 25 Change from Baseline to Week 26 in “total” UPDRS by Patient Cohort (Mean + SE)



Responder Analysis

The cumulative distribution of the change from baseline to week 26 in “total” UPDRS is demonstrated in Figure 5. Patients on 1 and 2 mg rasagiline showed almost identical distribution patterns. Half of the actively treated patients improved or remained unchanged (change in “total” UPDRS ≤ 0) compared to about 30% of placebo patients.

Figure 26 Cumulative Distribution of the Change from Baseline to Week 26 in “Total” UPDRS



The primary end-point was dichotomized according to the cut-off of 3 UPDRS points. Non-responders were defined as patients with a worsening of 3 or more points in “total” UPDRS. All other patients were considered responders. Logistic regression analysis was used to model responder status by treatment group, adjusting for baseline UPDRS (two contrasts). About two-thirds of rasagiline-treated patients but only approximately half of the placebo-treated patients were classified as responders at the end of the 26-week, placebo-controlled phase (Table 58). The difference between each one of the rasagiline groups and placebo was statistically

CLINICAL REVIEW

significant (1 mg vs. placebo: Odds Ratio 2.2, 95% CI [1.3, 3.7] $p = 0.0038$; 2 mg vs. placebo: Odds Ratio 2.5, 95% CI [1.4, 4.2] $p = 0.0011$ using Hochberg's Step-up Bonferroni procedure for multiple comparisons.

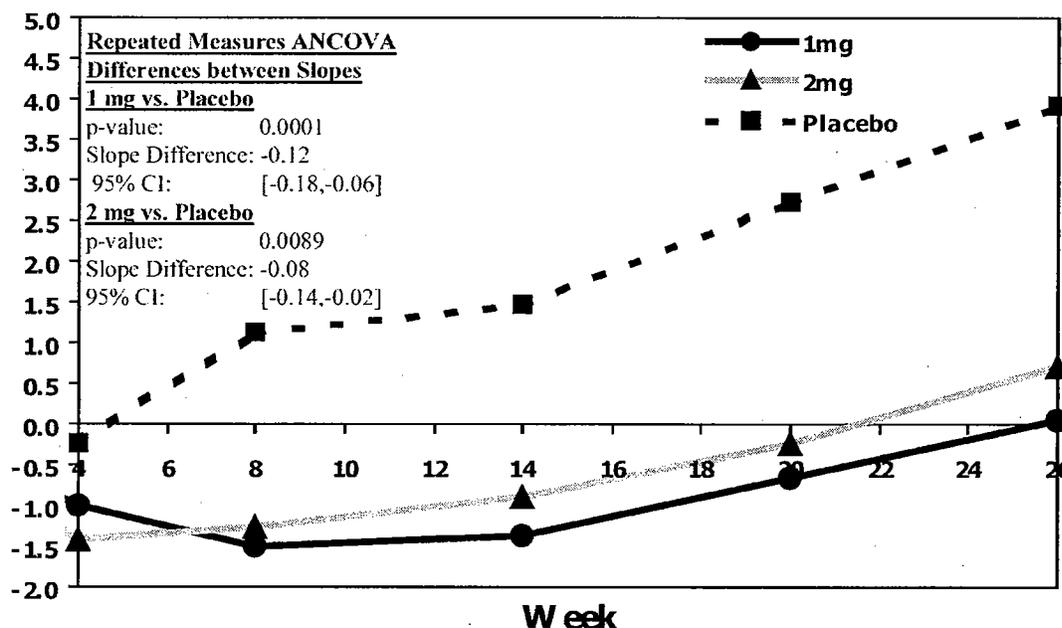
Table 58 Change from Baseline in "total" UPDRS < 3 Points – Responder Analysis

TVP-1012/232 Placebo-Controlled Phase	1 mg		2 mg		PLACEBO		All	
	N	%	N	%	N	%	N	%
Responder (UPDRS change<3)	88	65.7	88	66.7	68	49.3	244	60.4
Non-Responder (UPDRS change>=3)	46	34.3	44	33.3	70	50.7	160	39.6
All	134	100.0	132	100.0	138	100.0	404	100.0

Repeated Measures of the Change from Baseline in "Total" UPDRS Score

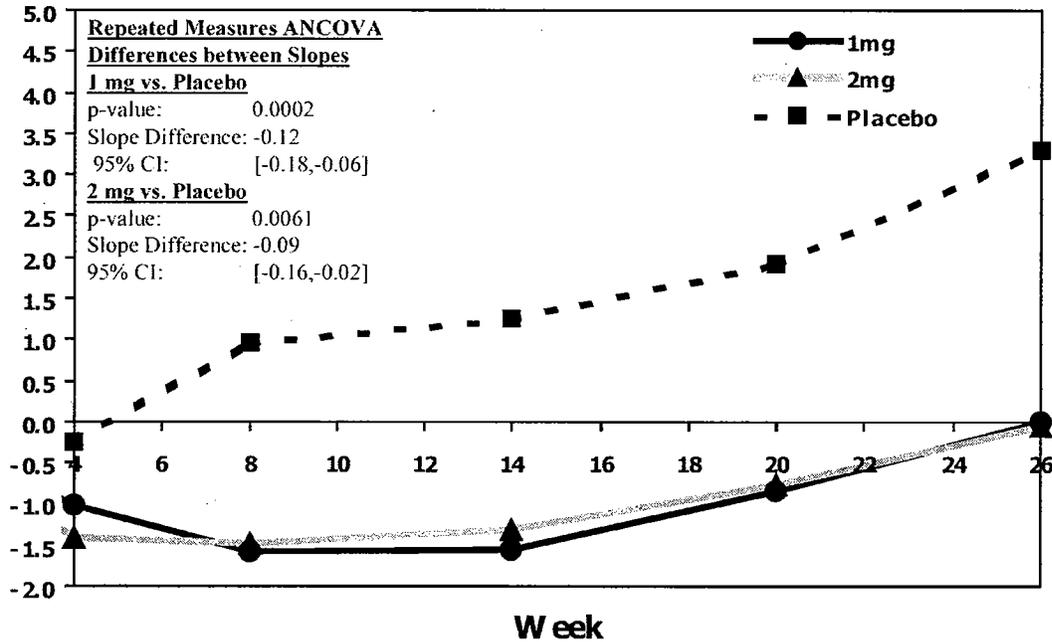
Repeated measure ANCOVA was employed to elucidate the mechanism and the time course of the drug effect. The mean change from baseline in "total" UPDRS is displayed using LOCF (Figure 27) and Actual Visit (Figure 28) approaches.

Figure 27 Mean Change from Baseline in "Total" UPDRS Score - LOCF



CLINICAL REVIEW

Figure 28 Mean Change from Baseline in “Total” UPDRS Score by Week on Treatment – Actual Visit



The difference between slopes for change from baseline in each active-treatment was significantly different from placebo. The estimated slope difference from placebo based on Actual Visit for the 1 mg group was -0.12 (95% CI: [-0.18, -0.06], $p = 0.0002$) and -0.09 (95% CI: [-0.16, -0.02], $p = 0.0061$) for the 2 mg group. The beneficial effect of either dose of rasagiline compared to placebo was evident starting at 4 weeks of treatment and was maintained throughout the remaining treatment duration.

Secondary End-Points

UPDRS Mental

The mean UPDRS Mental at baseline (Table 52) was higher ($p = 0.0123$) in the 2 mg group compared to the 1 mg and placebo groups. A trend toward positive treatment effect was observed at the end of the 26-week placebo-controlled phase but it did not reach statistical significance (i.e. $p < 0.05$). In the placebo group, a 0.34 point increase from baseline was observed in the mean UPDRS Mental scores as compared to 0.04 point decrease in the 2 mg group and a 0.15 point increase in the 2 mg group based upon LOCF imputation for the end of the 26 weeks. The effect of each treatment on the UPDRS mental score throughout the 26 weeks is shown using LOCF imputation (Table 59).

CLINICAL REVIEW

Table 59 Descriptive Statistics of UPDRS Mental Score at Baseline, Throughout Study, and Change from Baseline Using LOCF Imputation

TVP-1012/232 Placebo Controlled Phase		UPDRS Mental 1-4				UPDRS Mental 1-4 (Change)			
		1 MG	2 MG	PLACEBO	All	1 MG	2 MG	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	0.94	1.20	0.79	0.98	0.00	0.00	0.00	0.00
	Std	1.11	1.27	1.08	1.16	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Max	4.00	6.00	5.00	6.00	0.00	0.00	0.00	0.00
Week 4	N	134	132	138	404	134	132	138	404
	Mean	0.82	1.04	0.83	0.89	-0.12	-0.17	0.04	-0.08
	Std	1.16	1.46	1.09	1.25	1.23	1.00	0.79	1.02
	Min	0.00	0.00	0.00	0.00	-4.00	-4.00	-2.00	-4.00
	Max	7.00	7.00	4.00	7.00	6.00	4.00	2.00	6.00
Week 8	N	134	132	138	404	134	132	138	404
	Mean	0.86	1.09	0.89	0.95	-0.08	-0.11	0.10	-0.03
	Std	1.30	1.56	1.16	1.35	1.15	1.20	0.88	1.09
	Min	0.00	0.00	0.00	0.00	-4.00	-3.00	-3.00	-4.00
	Max	7.00	11.00	5.00	11.00	6.00	7.00	3.00	7.00
Week 14	N	134	132	138	404	134	132	138	404
	Mean	0.93	1.12	1.03	1.02	-0.01	-0.08	0.24	0.05
	Std	1.25	1.56	1.27	1.36	1.26	1.19	0.99	1.15
	Min	0.00	0.00	0.00	0.00	-3.00	-3.00	-3.00	-3.00
	Max	7.00	11.00	6.00	11.00	6.00	7.00	4.00	7.00
Week 20	N	134	132	138	404	134	132	138	404
	Mean	1.04	1.11	1.01	1.05	0.10	-0.09	0.22	0.08
	Std	1.34	1.52	1.25	1.37	1.26	1.23	0.90	1.14
	Min	0.00	0.00	0.00	0.00	-3.00	-4.00	-2.00	-4.00
	Max	7.00	11.00	5.00	11.00	6.00	7.00	3.00	7.00
26/Termination	N	134	132	138	404	134	132	138	404
	Mean	1.09	1.17	1.13	1.13	0.15	-0.04	0.34	0.15
	Std	1.52	1.53	1.40	1.48	1.50	1.25	1.06	1.29
	Min	0.00	0.00	0.00	0.00	-3.00	-4.00	-3.00	-4.00
	Max	10.00	11.00	6.00	11.00	10.00	7.00	4.00	10.00

UPDRS ADL

The mean UPDRS ADL score at baseline was comparable for all treatment groups. At the end of the 26-week treatment period, patients on both doses of rasagiline maintained mean ADL scores similar to baseline, while patients on placebo experienced an increase of about 19% in their mean ADL score. The effect of each treatment on the UPDRS ADL throughout the 26 weeks is shown using LOCF imputation (Table 60). UPDRS ADL and changes from baseline were similar based upon actual data collected. Compared to placebo, significant treatment effects were detected in the 1 mg/day (-1.04, 95% CI [-1.60, -0.48], $p = 0.0003$) and the 2 mg/day (-1.22, 95% CI [-1.79, -0.65] $p < 0.0001$) active-treatment groups using Hochberg's Step up Bonferroni procedure.

CLINICAL REVIEW

Table 60 Descriptive Statistics of UPDRS ADL Throughout Study and Change from Baseline Using LOCF for Missing Data

TVP-1012/232 Placebo-Controlled Phase		UPDRS ADL 5-17				UPDRS ADL 5-17 (Change)			
		1 MG	2 MG	PLACEBO	All	1 MG	2 MG	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	5.90	6.73	6.16	6.26	0.00	0.00	0.00	0.00
	Std	3.35	3.22	3.53	3.38	0.00	0.00	0.00	0.00
	Min	0.50	0.50	0.50	0.50	0.00	0.00	0.00	0.00
	Max	17.00	19.50	20.00	20.00	0.00	0.00	0.00	0.00
Week 4	N	134	132	138	404	134	132	138	404
	Mean	5.77	6.18	5.97	5.97	-0.13	-0.55	-0.18	-0.28
	Std	3.43	3.66	3.35	3.48	1.70	1.99	1.85	1.86
	Min	0.50	0.50	0.50	0.50	-5.00	-5.00	-6.00	-6.00
	Max	16.00	17.50	19.00	19.00	4.50	8.50	7.00	8.50
Week 8	N	134	132	138	404	134	132	138	404
	Mean	5.60	6.28	6.23	6.04	-0.30	-0.44	0.07	-0.22
	Std	3.25	3.68	3.87	3.62	2.18	2.05	2.55	2.28
	Min	0.50	0.50	0.50	0.50	-10.00	-5.00	-7.50	-10.00
	Max	17.00	23.50	19.00	23.50	6.50	8.50	11.50	11.50
Week 14	N	134	132	138	404	134	132	138	404
	Mean	5.79	6.28	6.61	6.23	-0.10	-0.45	0.45	-0.03
	Std	3.44	3.70	3.90	3.69	2.14	2.14	2.57	2.32
	Min	0.50	0.50	0.50	0.50	-8.00	-6.00	-6.50	-8.00
	Max	16.50	18.50	19.00	19.00	6.50	8.50	8.00	8.50
Week 20	N	134	132	138	404	134	132	138	404
	Mean	6.10	6.46	6.95	6.51	0.20	-0.27	0.79	0.25
	Std	3.50	3.81	4.00	3.78	2.45	2.37	2.47	2.46
	Min	0.50	0.00	0.50	0.00	-11.00	-5.50	-6.00	-11.00
	Max	19.00	21.00	19.00	21.00	6.50	8.50	7.50	8.50
26/Termination	N	134	132	138	404	134	132	138	404
	Mean	6.11	6.67	7.34	6.71	0.21	-0.06	1.18	0.45
	Std	3.61	3.82	4.10	3.88	2.57	2.39	2.48	2.53
	Min	0.50	0.00	0.50	0.00	-12.00	-7.00	-5.50	-12.00
	Max	19.00	19.50	19.00	19.50	10.00	8.50	9.50	10.00

UPDRS Motor

The mean UPDRS motor score at baseline was similar in all treatment groups. Following the 26-week placebo-controlled phase, mean UPDRS Motor score was not significantly different from baseline in patients on both rasagiline doses. UPDRS motor scores were increased by a mean of about 14% in placebo-treated patients (Table 61). Compared to placebo, the adjusted mean treatment effect was (-2.71, 95% CI [-3.87, -1.55] $p < 0.0001$) in patients treated with 1 mg/day and (-1.68, 95% CI [-2.85, -0.51] $p = 0.0050$) in patients treated with 2 mg/day rasagiline. The effect of each treatment on the UPDRS motor score throughout the 26 weeks is shown using LOCF imputation (Table 61). UPDRS Motor scores and changes from baseline were similar based actual data collected.

CLINICAL REVIEW

Table 61 Descriptive Statistics of UPDRS Motor Score Throughout Study and Change from Baseline Using LOCF for Missing Data

TVP-1012/232 Placebo-Controlled Phase		UPDRS Motor 18-44				UPDRS Motor 18-44 (Change)			
		1 MG	2 MG	PLACEBO	All	1 MG	2 MG	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	17.85	17.95	17.59	17.80	0.00	0.00	0.00	0.00
	Std	8.89	7.52	8.84	8.43	0.00	0.00	0.00	0.00
	Min	4.00	4.00	3.00	3.00	0.00	0.00	0.00	0.00
	Max	58.50	36.50	46.00	58.50	0.00	0.00	0.00	0.00
Week 4	N	134	132	138	404	134	132	138	404
	Mean	17.09	17.26	17.49	17.28	-0.76	-0.70	-0.10	-0.51
	Std	9.00	7.51	9.62	8.75	3.80	3.50	4.94	4.14
	Min	1.50	2.50	2.00	1.50	-12.00	-11.00	-20.50	-20.50
	Max	58.00	37.00	63.00	63.00	12.00	7.50	22.00	22.00
Week 8	N	134	132	138	404	134	132	138	404
	Mean	16.72	17.26	18.53	17.52	-1.13	-0.70	0.94	-0.28
	Std	9.13	8.15	10.27	9.25	4.20	3.98	5.29	4.62
	Min	2.00	2.50	2.50	2.00	-24.00	-13.50	-11.00	-24.00
	Max	49.00	39.00	63.00	63.00	10.00	10.00	22.00	22.00
Week 14	N	134	132	138	404	134	132	138	404
	Mean	16.60	17.59	18.38	17.53	-1.25	-0.36	0.79	-0.26
	Std	8.98	8.25	10.37	9.26	4.47	4.28	5.38	4.80
	Min	3.00	0.00	4.00	0.00	-21.50	-10.00	-15.50	-21.50
	Max	47.00	45.50	63.00	63.00	8.50	13.00	22.00	22.00
Week 20	N	134	132	138	404	134	132	138	404
	Mean	16.90	18.07	19.33	18.11	-0.95	0.11	1.74	0.31
	Std	9.67	8.54	10.81	9.76	4.74	4.34	5.83	5.13
	Min	0.50	1.00	2.00	0.50	-27.00	-13.00	-23.00	-27.00
	Max	58.50	41.50	63.00	63.00	12.00	12.00	22.00	22.00
26/Termination	N	134	132	138	404	134	132	138	404
	Mean	17.56	18.78	19.97	18.78	-0.29	0.82	2.38	0.98
	Std	9.53	9.03	10.78	9.85	4.92	4.46	6.29	5.40
	Min	1.50	2.50	2.00	1.50	-28.00	-13.50	-24.50	-28.00
	Max	45.50	39.00	63.00	63.00	11.50	14.00	22.00	22.00

Tremor, Rigidity, Bradykinesia and Postural Instability-Gait Disorder

Additional analysis suggested that a significant reduction in tremor (UPDRS items 16 and 20-26) was detected in the 1 mg/day treatment group compared to placebo, with a treatment effect of -0.63 (95% CI [-1.03, 0.23], $p = 0.002$). A marginal treatment effect was also observed in the 2 mg/day compared to placebo (-0.38, 95% CI: [-0.78, 0.02], $p = 0.0647$). Bradykinesia (items 32-39 and 44) was significantly reduced in both active-treatment groups. Compared to placebo, the treatment effect in the 1 mg/day group was -1.51 (95% CI [-2.19, -0.82], $p < 0.0001$) and -0.77 (95% CI [-1.47, -0.08], $p = 0.0285$) in the 2 mg/day group. A marginal treatment effect on rigidity (items 27-31) was detected in both doses of rasagiline compared to placebo. No treatment effect was detected for Postural Instability-Gait Disorder (PIGD) symptoms (items 13-15, 42 and 43).

CLINICAL REVIEW

Time to LD Therapy Need and the Proportion of LD-Free Patients

Patients who required LD during the placebo-controlled phase were withdrawn from that phase and were allowed to begin the active-treatment phase. The proportion of patients who did not need LD therapy at the end of the 26-week treatment period was similar in all treatment groups (88.8% in the 1 mg/day group and 83.3% in each of the other groups). No significant differences in time to LD need were detected between the treatment groups.

Change in Modified Hoehn and Yah Stage

The mean modified Hoehn and Yah Stage at baseline was similar for all treatment groups with a mean near two points (bilateral disease without impairment of balance). No changes were observed at termination for any treatment group.

Change in Schwab & England ADL Scale

Baseline assessment of Schwab & England ADL scale (rater and subject) showed that regardless of treatment group, mean ADL score was approximately 90%. This score indicates that the patients functioned independently with some difficulties and slowness. Following 26 weeks of treatment, no change was observed in ADL score in any group.

Exploratory End-Points

The sponsor did not make a distinction between secondary efficacy endpoints and exploratory efficacy endpoints. In response to a direct inquiry, the sponsor noted that there is no clear distinction. Secondary efficacy and exploratory efficacy endpoints had been identified as such in the protocol.

Clinical Global Impression of Change (CGIC)

The CGIC scale includes three sub-scales: Severity of Illness, Global Improvement and Efficacy Index.

Severity of Illness

The mean Severity of Illness score across treatment groups was similar at baseline (range 1.65 - 1.83) and indicated that, on average, patients were rated as "borderline to mildly ill". Following 26 weeks, an increase of 0.31 points (19%) in Severity of Illness score was observed in placebo-treated patients, but no significant change was detected in this parameter in either active treatment group. Compared to placebo (1.96), Severity of Illness score at termination was significantly lower in the 1 mg (1.78 ± 0.7 , $p = 0.009$) and 2 mg (1.81 ± 0.72 , $p = 0.001$) groups using Hochberg's Step-up Bonferroni procedure for multiple comparisons. The most pronounced deterioration in the placebo group was a shift from mildly to moderately ill experienced by 17 % of patients vs 4 % and 6 % of patients respectively in the 1 and 2 mg rasagiline groups.

Global Improvement and Efficacy Index

CLINICAL REVIEW

Following 26 weeks of treatment, a significantly greater proportion (73 %) of the 1 mg/day group ($p = 0.015$) and a marginally greater proportion (67 %) of the 2 mg/day group improved or remained unchanged compared to placebo (62 %).

Assessment of efficacy index (score of 1-16) takes into account the therapeutic effect (clinical improvement) together with the degree of side effects (the extent to which the side effects interfere with the patient functioning). Due to the large number (369) of patients reporting "no side effect interference with patient functioning" at termination visit, only the therapeutic effect score was analyzed. Minimal patient improvement as described by therapeutic effect score was observed in all treatments.

Timed Motor Test

Compared to baseline, no significant changes in Timed Motor Test score (in seconds) were detected at the 26-week Termination visit in any treatment group.

Quality of Life (QOL)

QOL questionnaires were distributed to the patients at Baseline, Week 14 and Termination (Week 26). At the Termination visit, QOL scores did not differ significantly from baseline in actively treated patients; a 9.6% increase from baseline in QOL score was observed in patients treated with placebo indicating deterioration in their QOL. Compared to placebo, a significant treatment effect was observed in patients treated with 1 mg/day (-2.91, 95% CI [-5.19, -0.64], $p = 0.0122$) and 2 mg/day (-2.74, 95% CI [-5.02, -0.45], $p = 0.0191$) rasagiline.

Beck Depression Inventory (BDI)

Mean baseline BDI score did not differ significantly by treatment group. At the week-26 termination visit, a 19% increase in BDI score was observed in the placebo group. This change was marginally different from the 7 % increase in the 1 mg/day and the 5 % increase in the 2 mg/day rasagiline groups.

ACTIVE-TREATMENT PHASE AND OVERALL STUDY RESULTS

Patient Disposition

From a "total" of 404 patients randomized into this study, 382 completed the placebo-controlled phase and 380 patients, distributed among 28 centers in the US and 4 centers in Canada continued on to the active-treatment phase. Most patients (87 - 90 %) from each treatment were studied in the U.S. No randomization procedure was used. Patients originally randomized to 1 or 2 mg/day rasagiline during the placebo-controlled phase maintained the same dose during the active-treatment phase, while placebo-treated patients switched to 2 mg/day rasagiline and are therefore termed "placebo/2 mg."

CLINICAL REVIEW

Approximately 81 % (326) of the patients who had been randomized into the double-blinded, placebo-controlled phase and who had completed the 26-week placebo-controlled phase entered the active-treatment phase. In addition, 54 patients who had required additional anti-PD therapy, were consequently withdrawn from the placebo-controlled phase and started the active-treatment phase according to protocol. Table 62 shows the distribution of patients among the different treatment groups of the placebo-controlled phase who did or did not require additional anti-PD therapy during that phase.

During the active treatment phase, 269 patients (71%) were able to be maintained on rasagiline alone (monotherapy) and 111 (29%) patients required additional anti-PD therapy during this active treatment phase. Table 63 shows the distribution of patients among the different treatment groups of the active treatment phase who did or did not require additional anti-PD therapy during that phase.

For the 360 patients who completed the active-treatment phase, the percentage (92 – 97 %) of completers was similar in all 3 groups. Table 64 summarizes termination reasons by treatment group and shows that there was no striking differences in reasons for study termination. Survival (Kaplan-Meier) of the time to last dose were compared using the Log-Rank Test and there were no statistically significant differences.

Table 62 Distribution of Patients by their Need for Additional Anti-Parkinson's Disease Therapy during the Placebo-Controlled Phase

TVP-1012/232 Active-Treatment Phase	Treatment Group						All	
	1 mg		2 mg		Placebo/2 mg		N	%
	N	%	N	%	N	%		
All	124	100.0	124	100.0	132	100.0	380	100.0
Did not Need Additional Therapy in PC* Phase	110	88.7	105	84.7	111	84.1	326	85.8
Needed Additional Therapy in PC Phase	14	11.3	19	15.3	21	15.9	54	14.2

*Placebo-Controlled

Table 63 Distribution of Patients by their Need for Additional Anti-Parkinson's Disease Therapy during the Active-Treatment Phase

TVP-1012/232 Active-treatment Phase	1 mg		2 mg		Placebo/2 mg		All	
	N	%	N	%	N	%	N	%
All	124	100.0	124	100.0	132	100.0	380	100.0
Started Additional Therapy								
No	90	72.6	84	67.7	95	72.0	269	70.8
Yes	34	27.4	40	32.3	37	28.0	111	29.2

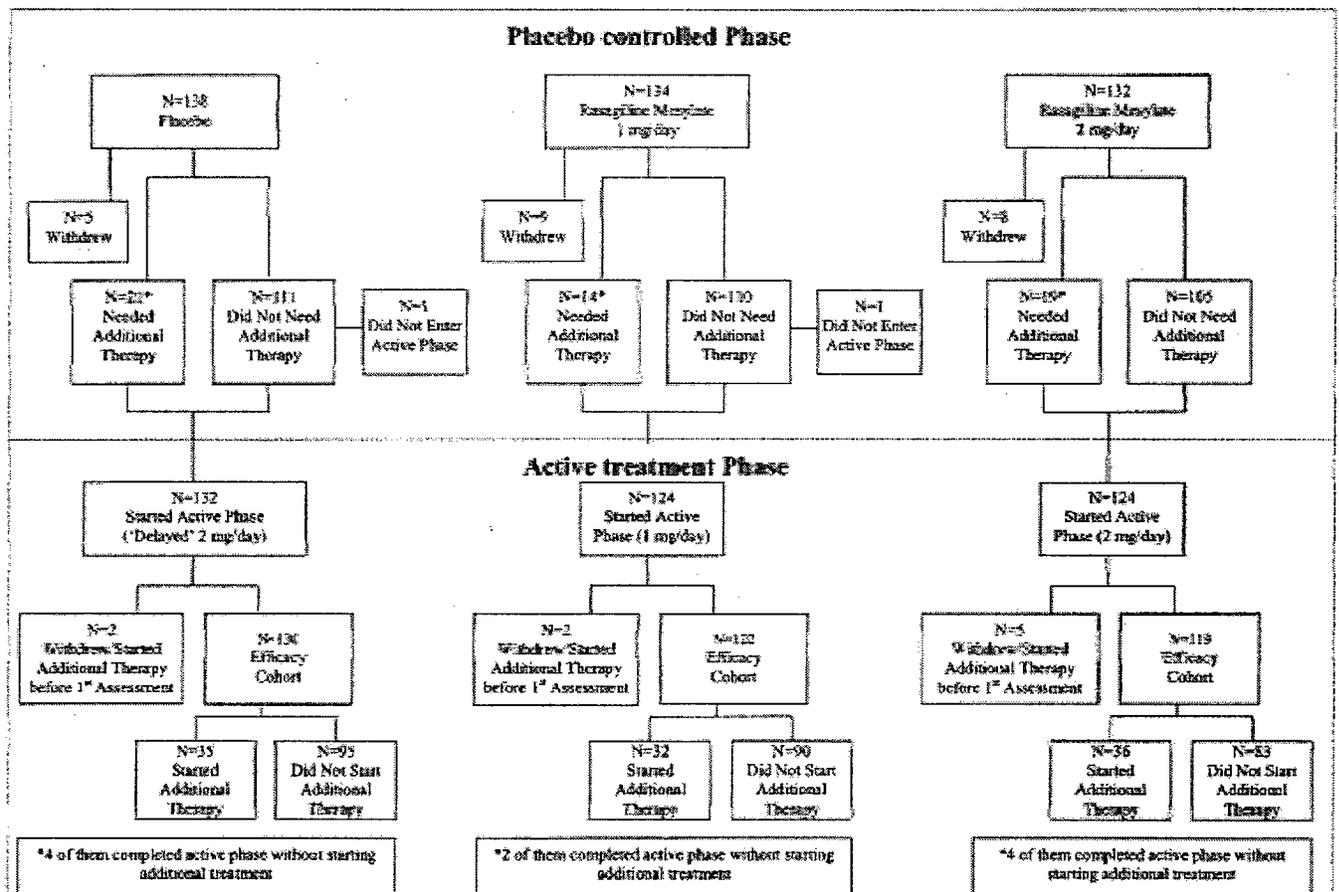
CLINICAL REVIEW

Table 64 Distribution of Patients by Termination Reason

TVP-1012/232 Active-Treatment Phase	Treatment Group						All	
	1 mg		2 mg		Placebo/2 mg			
	N	%	N	%	N	%	N	%
All	124	100.0	124	100.0	132	100.0	380	100.0
Termination Reason:								
Normal Completion	120	96.8	118	95.2	122	92.4	360	94.7
Adverse Event	.	.	2	1.6	3	2.3	5	1.3
Subject Request	2	1.6	3	2.4	4	3.0	9	2.4
Unsatisfactory Response	1	0.8	1	0.3
Other	2	1.6	1	0.8	2	1.5	5	1.3

Figure 29 shows the disposition of all Patients in the Placebo-Controlled Phase and Active Treatment Phase.

Figure 29 Disposition of All Patients in the Placebo-Controlled Phase and Active Treatment Phase



CLINICAL REVIEW

Datasets Analyzed : Patient Cohorts

The following cohorts were identified for the purpose of data presentation and statistical analysis : 1) Active-Treatment Cohort: includes all patients who have entered the active-treatment phase (380 patients); and 2) Efficacy Cohort: includes all patients with at least one UPDRS measurement in the active-treatment phase, before the onset of additional anti-PD therapy (371 patients).

The percentage (96 -99 %) of patients in the efficacy cohort was similar in all 3 groups.

Baseline Characteristics (Active-Treatment Cohort)

There were no substantive differences in demographic characteristics, baseline Parkinson's Disease symptoms at diagnosis, or mean disease duration among the 3 treatment groups. The comorbidities (previous and concomitant illnesses) at screening were not considered to have effects on study treatment.

Concomitant and Previous Medications

The majority of patients consumed concomitant medications during the active-treatment phase. The most commonly used medications, reported by more than 60% of study participants, included analgesics and anti-inflammatory agents as well as nutritional agents and vitamins. Cardiovascular agents, dopaminergic agents and gastrointestinal agents were also frequently used (reported by 30-40% of the patients). For the 3 treatment groups, there were no striking nor noteworthy differences in the incidence of concomitant medications used in the active treatment phase nor in the incidence of previous medications by drug class.

Measurements of Treatment Compliance

Study drug compliance was estimated by calculating the amount of drug required, assuming compliance with protocol drug intake; number of tablets dispensed and number of tablet returned and number of days in the study phase. Approximately 98 % of patients in each treatment group was considered to be compliant with treatment.

Efficacy Results

Of the 380 patients who entered the active-treatment phase (active-treatment cohort), nine patients (1 mg, n= 2, 2 mg, n= 2; placebo/2 mg, n= 5) who received additional dopaminergic therapy or withdrew immediately following entrance to active-treatment phase (before the first efficacy assessment) were not included in the efficacy analysis. The other 371 patients (92%) were included in the efficacy analysis (efficacy cohort) of the active-treatment phase.

“Total” UPDRS Score and Change from Baseline to Last Observed Value

For each visit conducted before the beginning of actual additional therapy, changes in “total” UPDRS score were computed from baseline visit (Week 0, beginning of double-blind, placebo-

CLINICAL REVIEW

controlled phase) as well as Week 26, termination of double-blind, placebo-controlled phase and initiation of active-treatment phase.

The mean and median change in “total” UPDRS from baseline for each treatment group is shown in Table 65. The 52-week mean (± SD) changes from baseline were 3.01 (8.26), 1.97 (7.49) and 4.17 (8.83) for the 1 mg, 2 mg and placebo/2 mg treatment groups, respectively. Mean changes in “total” UPDRS over time are shown for the different treatment groups in Figure 30. The difference between each of the long-term rasagiline treatment groups (1 and 2 mg) and the placebo/2 mg group (two contrasts) was statistically significant ($p = 0.046$ and $p = 0.024$, respectively). Due to the influence of outlier patients (especially patient #198 in the 1 mg group), non-parametric testing was used. The median changes from baseline were 3, 1.5 and 3.5 for the 1, 2 and placebo/2 mg treatment groups, respectively. The difference gained between the placebo and 2 mg group at the end of the placebo-controlled phase (Week 26) was sustained for additional 26 weeks despite the fact that both groups were treated with 2 mg rasagiline during that period. This difference was statistically significant (Figure 31, $p = 0.024$).

“Total” UPDRS Score and Change from Baseline by Visit

The LOCF imputation was applied to account for missing data, early discontinuation and for measurements taken after the initiation of additional anti-PD therapy. Both 1 and 2 mg rasagiline dosages exhibited a sustained clinical effect at each visit during the active-treatment phase. The group who switched from placebo to 2 mg/day rasagiline had an initial decrease in “total” UPDRS score which diminished thereafter. Following 26 weeks of treatment with rasagiline, the mean and median “total” UPDRS scores of patients with delayed treatment onset. (placebo/2 mg) remained similar to their “Week 26” baseline (Figure 30 and Figure 31).

Table 65 “Total” UPDRS at Baseline and Change from Baseline or from Week 26

TVP-1012/232 Tempo		Total UPDRS				Total UPDRS (Change from Baseline)				Total UPDRS (Change from Week 26)			
		1 mg	2 mg	Placebo/2mg	All	1 mg	2 mg	Placebo/2mg	All	1 mg	2 mg	Placebo/2mg	All
Week 0 (Baseline)	N	124	124	132	380								
	Mean	24.52	25.44	23.77	24.56								
	Median	22.25	24.00	21.75	23.00								
Week 26/Placebo-Controlled Phase Termination	N	124	122	132	378	124	122	132	378				
	Mean	24.50	25.80	27.59	26.00	-0.03	0.50	3.82	1.49				
	Median	22.50	24.00	24.75	24.00	0.25	0.00	3.00	1.00				
Week 52/Last visit before Additional Therapy	N	122	119	130	371	122	119	130	371	122	119	130	371
	Mean	27.45	27.10	28.02	27.54	3.01	1.97	4.17	3.08	2.92	1.47	0.45	1.59
	Median	27.50	26.50	24.25	26.50	3.00	1.50	3.50	2.50	2.00	1.00	0.00	1.50

CLINICAL REVIEW

Figure 30 Mean Change from Baseline in "Total" UPDRS (LOCF)

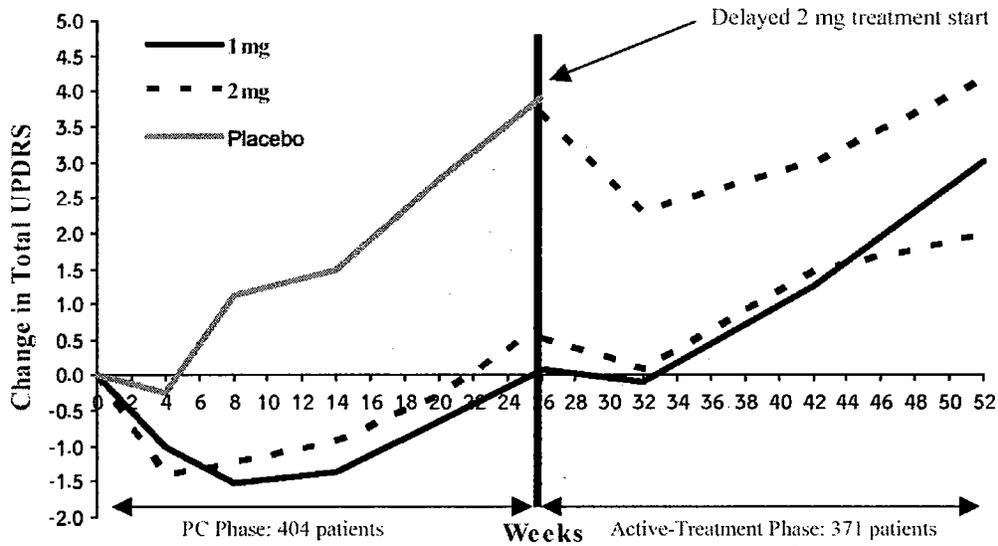
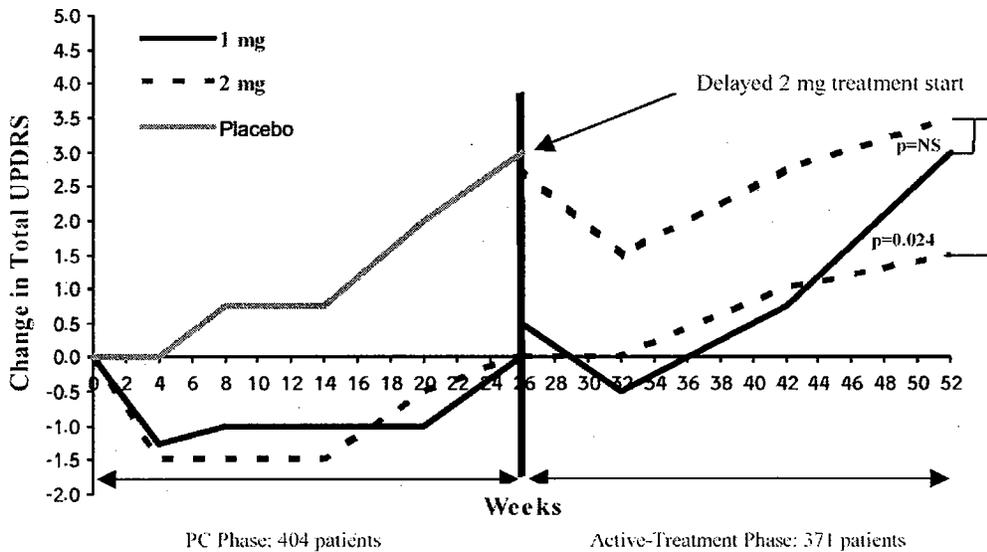


Figure 31 Median Change from Baseline in "Total" UPDRS (LOCF)



CLINICAL REVIEW

Table 66 Efficacy Cohort : Descriptive Statistics of “Total” UPDRS and Change from Baseline During the Entire Study by Scheduled Visit for Enrollees of the Active Treatment Phase (LOCF in each phase)

TVP-1012/232 Tempo		Total UPDRS				Total UPDRS (Change)			
		1 mg	2 mg	Placebo/2mg	All	1 mg	2 mg	Placebo/2mg	All
Baseline	N	122	119	130	371	122	119	130	371
	Mean	24.45	25.12	23.85	24.45	0.00	0.00	0.00	0.00
	Median	22.00	24.00	21.75	23.00	0.00	0.00	0.00	0.00
	Std	11.53	9.12	10.87	10.56	0.00	0.00	0.00	0.00
	Min	5.50	10.50	5.50	5.50	0.00	0.00	0.00	0.00
	Max	75.00	53.50	57.00	75.00	0.00	0.00	0.00	0.00
Week 4	N	122	119	130	371	122	119	130	371
	Mean	23.40	23.26	23.48	23.38	-1.05	-1.86	-0.37	-1.07
	Median	21.50	22.00	21.50	21.50	-1.50	-1.50	0.00	-1.00
	Std	11.88	9.20	10.88	10.70	4.56	3.95	5.21	4.65
	Min	3.50	3.50	5.50	3.50	-15.00	-11.50	-17.50	-17.50
	Max	75.50	50.00	58.50	75.50	11.00	9.00	12.50	12.50
Week 8	N	122	119	130	371	122	119	130	371
	Mean	22.91	23.51	24.80	23.77	-1.53	-1.61	0.95	-0.69
	Median	20.50	22.00	22.00	22.00	-1.25	-2.00	0.00	-1.00
	Std	11.74	10.41	12.32	11.54	5.34	5.04	6.20	5.68
	Min	3.50	3.50	5.00	3.50	-31.00	-18.00	-12.50	-31.00
	Max	62.50	61.00	70.00	70.00	11.50	14.00	25.50	25.50
Week 14	N	122	119	130	371	122	119	130	371
	Mean	23.07	23.89	25.08	24.04	-1.38	-1.23	1.23	-0.42
	Median	21.75	23.00	22.25	22.50	-1.00	-2.00	0.50	-0.50
	Std	11.56	10.28	12.47	11.50	5.91	5.17	6.35	5.96
	Min	3.50	1.00	5.00	1.00	-27.50	-11.50	-14.50	-27.50
	Max	61.50	53.50	64.50	64.50	12.00	12.00	21.00	21.00
Week 20	N	122	119	130	371	122	119	130	371
	Mean	23.94	24.54	26.34	24.97	-0.50	-0.58	2.49	0.52
	Median	21.75	24.00	23.50	22.50	-0.75	-0.50	2.00	0.00
	Std	12.55	10.83	13.01	12.21	6.37	5.75	6.86	6.51
	Min	3.50	3.00	6.50	3.00	-37.00	-14.50	-19.00	-37.00
	Max	75.00	57.00	66.50	75.00	15.00	16.00	24.00	24.00
Week 26 (PC* Termination)	N	122	119	130	371	122	119	130	371
	Mean	24.54	25.63	27.56	25.95	0.09	0.51	3.71	1.49
	Median	22.50	24.00	24.75	24.00	0.50	0.00	2.75	1.00
	Std	12.30	11.48	13.33	12.45	6.58	5.87	7.36	6.83
	Min	4.00	3.50	5.00	3.50	-39.00	-14.00	-18.50	-39.00
	Max	60.00	58.00	65.00	65.00	13.50	21.00	23.50	23.50
Week 32	N	122	119	130	371	122	119	130	371
	Mean	24.36	25.22	26.16	25.27	-0.09	0.10	2.31	0.81
	Median	23.25	23.00	22.50	23.00	-0.50	0.00	1.50	0.50
	Std	13.67	11.37	13.57	12.93	7.76	6.58	7.85	7.50
	Min	2.50	3.00	3.50	2.50	-44.50	-12.50	-25.00	-44.50
	Max	78.00	59.00	64.50	78.00	20.50	30.50	28.00	30.50
Week 42	N	122	119	130	371	122	119	130	371
	Mean	25.71	26.58	26.85	26.39	1.27	1.46	3.00	1.93
	Median	24.00	24.50	24.00	24.00	0.75	1.00	2.75	1.50
	Std	13.24	11.76	13.62	12.90	6.93	6.94	7.98	7.34
	Min	3.50	6.00	6.00	3.50	-30.00	-12.50	-18.00	-30.00
	Max	80.50	70.00	69.00	80.50	20.50	43.50	38.00	43.50
Week 52	N	122	119	130	371	122	119	130	371
	Mean	27.45	27.10	28.02	27.54	3.01	1.97	4.17	3.08
	Median	27.50	26.50	24.25	26.50	3.00	1.50	3.50	2.50
	Std	14.18	11.90	14.17	13.46	8.26	7.49	8.83	8.26
	Min	2.50	3.50	3.50	2.50	-37.00	-12.50	-19.00	-37.00
	Max	70.00	70.00	69.00	70.00	27.50	43.50	45.00	45.00

*Placebo-Controlled phase

CLINICAL REVIEW

“Total” UPDRS Score and Area under the Curve (AUC) Analysis

The median values of the change from baseline in “total” UPDRS. AUC (Week 26-52) were identical in both 1 and 2 mg rasagiline groups (23.5) and three-fold higher (representing a more severe Parkinson’s disease stage) in the placebo/2 mg group (Table 67). The AUC/Week in the placebo/2 mg treatment group was significantly greater than the 1 mg ($p = 0.015$) and 2 mg ($p = 0.003$) groups.

Table 67 Descriptive Statistics of Change from Baseline in “Total” UPDRS AUC Adjusted and Mean Change from baseline from Week 26 to 52 (LOCF)

TVP-1012/232 Active-treatment Phase	AUC				AUC*				Mean Change from Baseline			
	1 mg	2 mg	Placebo/2 mg	All	1 mg	2 mg	Placebo/2 mg	All	1 mg	2 mg	Placebo/2 mg	All
N	122	119	130	371	122	119	130	371	122	119	130	371
Mean	27.29	26.79	80.42	45.74	1.05	1.03	3.09	1.76	1.07	1.01	3.30	1.83
Median	23.50	23.50	70.00	41.50	0.90	0.90	2.69	1.60	0.56	0.75	2.75	1.63
Std	175.61	162.01	193.75	179.43	6.75	6.23	7.45	6.90	6.64	6.04	7.29	6.77
Min	-958.00	-304.00	-530.50	-958.00	-36.85	-11.69	-20.40	-36.85	-37.63	-11.25	-20.13	-37.63
Max	477.50	959.50	895.00	959.50	18.37	36.90	34.42	36.90	15.88	34.63	33.25	34.63

*Divided by 26 to reflect mean change from Baseline per Week

Because all patients were receiving rasagiline for six weeks when assessed at Week 32, the symptomatic effects of the drug were presumably balanced at that time for all treatment groups. To isolate the symptomatic effect of rasagiline, the AUC of the change from baseline was evaluated for the period of Week 32-52. The median AUC values were similar in the 1 and 2 mg rasagiline groups (21.3 and 22.5, respectively) and about 2.5-fold higher in the placebo/2 mg group. The AUC/Week of the change from baseline was 1.06, 1.13 and 2.63 for the 1, 2 and placebo/2 mg groups, respectively. The change from baseline in the placebo/2 mg group to the mean of Weeks 32, 42 and 52 was significantly greater than the 2 mg ($p = 0.0086$) treatment group. For the 1 mg treatment group, it did not reach statistical significance ($p = 0.0605$).

Subgroup Analyses

Subpopulation analysis of the TEMPO Study (TVP-1012/232) placebo-controlled phase was carried out for age groups (age categorized as <65 years vs. = 65 years) and sex for the primary endpoint (change from baseline to last observed value in total UPDRS score) and selected secondary endpoints (change from baseline to last observed value in the UPDRS ADL and UPDRS motor scores).

The statistical model for each one of these endpoints is similar to the model specified in the Statistical Analysis Plan of the study, with the following changes: age category and sex were added to the original model as fixed effects, and tests of homogeneous treatment effect between geriatric and non-geriatric patients and between male and female were performed using treatment-by-age category and treatment by sex interaction terms.

CLINICAL REVIEW

No difference in change from baseline in “total” UPDRS and its subscales was detected between age categories and between male and female. Furthermore, the treatment by age interaction and treatment by sex interaction were found to be non-significant, indicating homogeneous treatment effect for geriatric versus non-geriatric patients as well as male versus female.

There were no subgroup analyses for race because most patients enrolled were Caucasians.

Table 68 Tempo Placebo-Controlled Phase : Descriptive Statistics of “Total” UPDRS at Baseline, Termination and Change from Baseline by Age Category

Rasagiline ISE: Placebo-Controlled Studies Without Levodopa Treatment		Age Category								All			
		Less than 65 years				65 years or more							
		Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All	Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All	Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All
UPDRS Total (Baseline)	N	74	72	80	226	60	60	58	178	134	132	138	404
	Mean	23.11	25.24	23.84	24.05	26.63	26.67	25.50	26.28	24.69	25.89	24.54	25.03
	Std	11.33	10.49	12.01	11.30	10.92	8.27	11.06	10.11	11.25	9.54	11.61	10.84
	Median	20.25	23.00	21.25	21.75	24.50	26.25	22.50	24.50	22.75	24.25	22.00	23.00
	Min	8.00	10.50	5.50	5.50	5.50	11.50	7.00	5.50	5.50	10.50	5.50	5.50
UPDRS Total (Termination)	N	74	72	80	226	60	60	58	178	134	132	138	404
	Mean	23.19	25.35	27.59	25.44	26.68	28.13	29.61	28.12	24.75	26.61	28.44	26.62
	Std	11.48	11.97	14.31	12.78	13.00	11.58	14.33	12.98	12.26	11.83	14.30	12.92
	Median	21.75	23.25	24.00	23.25	24.50	27.75	27.00	22.75	24.50	22.75	25.50	24.50
	Min	5.00	3.50	6.50	3.50	4.00	4.50	5.00	4.00	4.00	3.50	5.00	3.50
UPDRS Total (Change)	N	74	72	80	226	60	60	58	178	134	132	138	404
	Mean	0.07	0.11	3.76	1.39	0.05	1.46	4.11	1.85	0.06	0.72	3.91	1.59
	Std	8.04	5.56	7.55	7.34	4.98	6.08	7.36	6.39	6.82	5.82	7.45	6.93
	Median	0.75	-0.25	2.50	1.00	-0.50	0.75	3.25	1.50	0.00	0.00	3.00	1.00
	Min	-39.00	-14.00	-18.50	-39.00	-11.00	-12.50	-11.00	-12.50	-39.00	-14.00	-18.50	-39.00
Max	26.00	21.00	22.00	26.00	10.00	16.00	23.50	23.50	26.00	21.00	23.50	26.00	

Table 69 Tempo Placebo-Controlled Phase : Descriptive Statistics of “Total” UPDRS at Baseline, Termination and Change from Baseline by Sex/Gender

Rasagiline ISE: Placebo-Controlled Studies Without Levodopa Treatment		Sex								All			
		Male				Female							
		Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All	Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All	Rasagiline 1 mg	Rasagiline 2 mg	Placebo	All
UPDRS ADL (Baseline)	N	90	74	93	257	44	58	45	147	134	132	138	404
	Mean	5.90	6.45	6.32	6.21	5.90	7.08	5.82	6.34	5.90	6.73	6.16	6.26
	Std	3.38	3.17	3.42	3.33	3.34	3.27	3.48	3.35	3.22	3.53	3.38	3.38
	Median	5.25	6.50	5.50	6.00	5.00	6.50	5.50	6.00	5.00	6.50	5.50	6.00
	Min	0.50	0.50	0.50	0.50	0.50	0.50	1.00	0.50	0.50	0.50	0.50	0.50
UPDRS ADL (Termination)	N	90	74	93	257	44	58	45	147	134	132	138	404
	Mean	6.04	6.67	7.58	6.78	6.25	6.66	6.86	6.60	6.11	6.67	7.34	6.71
	Std	3.47	3.71	3.98	3.77	3.92	3.99	4.36	4.07	3.61	3.82	4.10	3.88
	Median	6.00	6.25	7.00	6.50	6.00	6.00	5.50	6.00	6.00	6.00	7.00	6.00
	Min	0.50	1.00	0.50	0.50	0.50	0.00	1.00	0.00	0.50	0.00	0.50	0.00
UPDRS ADL (Change)	N	90	74	93	257	44	58	45	147	134	132	138	404
	Mean	0.14	0.22	1.26	0.57	0.35	-0.41	1.03	0.26	0.21	-0.06	1.18	0.45
	Std	2.75	1.97	2.38	2.46	2.19	2.82	2.71	2.66	2.57	2.39	2.48	2.53
	Median	0.00	0.00	1.00	0.50	0.00	-0.50	1.00	0.00	0.00	0.00	1.00	0.50
	Min	-12.00	-4.00	-5.00	-12.00	-3.50	-7.00	-5.50	-7.00	-12.00	-7.00	-5.50	-12.00
Max	6.50	7.00	8.00	8.00	10.00	8.50	9.50	10.00	10.00	8.50	9.50	10.00	

CLINICAL REVIEW

11.1.2. Sponsor's Discussion of All Results (Placebo-Controlled and Active Treatment Phase) of TVP-1012/232 TEMPO

Four-hundred and four (404) patients with early PD were enrolled in the study at 32 centers. Each participant was randomized to treatment with 1 mg/day or 2 mg/day rasagiline or placebo. The study drug was taken once daily. A delayed-start design was employed in this study which can be used to separate an immediate symptomatic effect from a true effect on disease progression. In this design, 2/3 of the patients began rasagiline treatment at the start of the study (placebo-controlled phase). The remaining subjects were treated with placebo for six months followed by six months with rasagiline 2 mg/day (active-treatment phase). At baseline visit, the groups were similar in terms of sex, age, severity of PD and disability. Baseline study cohort characteristics (ITT) were similar to those in other studies enrolling PD patients with insufficient disability to require levodopa therapy. The ITT cohorts of both study phases had similar demographic and baseline disease characteristics. Significant differences were not found across treatment groups in active-treatment phase participants.

Three-hundred eighty-two (382) patients completed the placebo-controlled phase. Twenty-two patients (9, 8 and 5 in the 1 mg, 2 mg and placebo groups, respectively) prematurely discontinued from this phase; of these, 8 (2%) patients (5, 2 and 1, respectively) discontinued due to AEs. A "total" of 380 patients continued on to the active-treatment phase. Three-hundred and sixty (360) patients completed the active-treatment phase and 20 patients (4, 6 and 10 in the 1 mg, 2 mg and placebo/2 mg groups, respectively) did not complete this phase. There were 5 (1.3%) patients (0, 2 and 3, respectively in the 1 mg, 2 mg, and placebo/2 mg groups) who withdrew due to adverse events. Of the 380 patients who continued on to the active-treatment phase, 54 required additional anti-PD therapy during the placebo-controlled phase. A "total" of 269 (71%) completed the active-treatment phase on rasagiline alone ("monotherapy") and the rest used rasagiline concomitantly with anti-PD medications.

In early stage PD patients, a six-month course of rasagiline therapy was associated with a significant reduction in the adjusted mean change from baseline in "total" UPDRS scores compared to placebo (-0.13, +0.51 and +4.07 for the 1, 2 and placebo treatment groups, respectively). Rasagiline treatment was associated with a clinical benefit in terms of other endpoints relevant to PD symptomatology and treatment, and maintenance of baseline QOL level in contrast to the deterioration observed in the placebo group. The treatment effect was similar for both rasagiline doses. The mean changes from baseline (Week 0) until the termination visit in the active treatment phase in "total" UPDRS scores for the combined placebo-controlled phase (< 26 weeks) and the active treatment phase (< 26 weeks) were 3.01, 1.97, and 4.17, for the 1 mg, 2 mg and placebo/2 mg treatment groups, respectively. The difference between each of the long-term rasagiline treatment groups and the placebo/2 mg group (two contrasts) was statistically significant.

Median changes from baseline were 3, 1.5 and 3.5 for the 1, 2 and placebo/2 mg groups, respectively; the difference between the 2 mg group and the placebo/2 mg group was statistically significant. The sponsor noted that this decline is considerably smaller than the reported decline seen in placebo arms in a similar stage of PD participating in other controlled

CLINICAL REVIEW

clinical trials. The reported annual rate of PD worsening in placebo treatment groups was 8-14 “total” UPDRS scores.

In the initial 6 month placebo-controlled phase, the symptomatic effects of 1 and 2 mg/day rasagiline were comparable and significantly different from placebo. Because all patients were receiving rasagiline in the second phase of the study, the symptomatic effects of the drug were presumably balanced for all treatment groups at the time of last evaluation. Thus, the differences in performance observed at the final visit cannot be fully explained by symptomatic effects of rasagiline.

The beneficial treatment effect exerted by rasagiline 2 mg/day during the six-month, placebo-controlled phase was reproducible since a similar effect was demonstrated during the active-treatment phase of the study in patients who initially were treated with placebo.

11.1.3. Sponsor’s Conclusions of TVP-1012/232 TEMPO

Compared to placebo, a six-month course of treatment of with 1 mg/day or 2 mg/day rasagiline was associated with a significant reduction in the adjusted mean change from baseline in “total” UPDRS score in early stage PD patients. This treatment benefit was driven by the ADL and Motor sub-scales of this assessment. Furthermore, rasagiline was associated with a clinical benefit in terms of other endpoints relevant to PD symptomatology and treatment, and maintenance of baseline QOL level in contrast to the deterioration observed in the placebo group. The treatment effect was similar in both rasagiline doses (1 and 2 mg/day).

This trial shows that patients treated with rasagiline at dosages of 1 and 2 mg/day for one year had less progression in “total” UPDRS scores than patients for whom rasagiline treatment (2 mg/d) was delayed for six months. The effect of one year rasagiline 2 mg/day treatment was statistically significant in comparison with delayed rasagiline treatment for 6 months, and was detected over a relatively short period of observation. The results cannot be explained by a purely symptomatic effect of rasagiline. The effect of one year rasagiline 1 mg/day treatment tended to have greater clinical benefit in comparison with delayed rasagiline 2 mg/day treatment for 6 months. The beneficial treatment effect exerted by rasagiline 2 mg/day during the placebo-controlled phase was reproduced in patients for whom rasagiline treatment was delayed for six months. Moreover, treatment with rasagiline over one year resulted in sustained clinical improvement of Parkinsonian symptoms.

11.1.4. Reviewer’s Comments on Sponsor’s Results

- I have commented or summarized results in this section when I have noted something that differs from the sponsor’s description or summary of results. I have also presented my own discussion of any issues I have deemed worthy of discussion. In addition, I have provided my own conclusions about the efficacy of rasagiline.

CLINICAL REVIEW

Placebo-Controlled Phase

- The separate analysis of the primary efficacy endpoint (i.e. “total” UPDRS change baseline to termination visit of placebo-controlled phase, by the statistical reviewer (Dr. Sharon Yan) confirmed the same values for the 3 treatment groups as presented by the sponsor. Dr. Yan’s analysis also confirmed sponsor’s reported primary analysis of this primary efficacy endpoint using ANCOVA adjusted for baseline UPDRS, treatment, center and treatment-by-center interaction. Of interest, Dr. Yan’s analyses showed differences (Table 54 vs Table 70) in her calculations of “total” UPDRS and change from baseline for all of the values for all 3 treatment groups at various visits (week 4, 8, 14, 20) between baseline and the week 26 or termination visit. Overall, these differences were relatively minor and Dr. Yan’s statistical analyses (without adjusting for the multiple comparisons) showed nominal p values that were highly statistically ($p = 0.0001$) in most instances. Although the explanation for the different values is not completely clear, the explanation may have something to do with the observation that Dr. Yan noted whereby a few patients who dropped out of the placebo-controlled phase before the first efficacy visit (week 4) appeared to have their “total” UPDRS score data (? baseline scores) carried forward throughout the study. In contrast, Dr. Yan’s calculations did not carry forward a UPDRS score that was not collected post-treatment.

Table 70 Analyses of DNDP Statistical Reviewer for “Total” UPDRS and Change from Baseline Using LOCF Imputation During Double-Blinded, Placebo-Controlled Phase

	Rasagiline 1 mg (n=134)			Rasagiline 2 mg (n=132)			Placebo (n=138)	
	Mean	Mean Change	p-value	Mean	Mean Change	p-value	Mean	Mean Change
Baseline	24.69			25.87			24.54	
Week 4	23.57	-1.12	0.1394	24.01	-1.68	0.0066	23.83	-0.42
Week 8	23.16	-1.53	0.0001	24.45	-1.44	0.0001	25.43	0.89
Week 14	23.21	-1.48	0.0001	24.48	-1.24	0.0001	25.66	1.12
Week 20	23.92	-0.77	0.0001	24.87	-1.02	0.0001	26.82	2.28
Week 26 (Termination)	24.75	0.06	0.0001	26.61	0.72	0.0001	28.44	3.91

The primary statistical analysis of the primary efficacy endpoint showed a robust therapeutic effect of rasagiline (Figure 24). Overall, analyses for each dose of rasagiline suggested that 1 mg/day and 2 mg/day were both therapeutic and that there was no clear benefit of the higher dose. In contrast, most analyses of the primary efficacy measure (change in baseline “total” UPDRS) at various timepoints and many of the analyses of the secondary efficacy endpoints showed that results of the 1 mg rasagiline dose were usually numerically superior to results of the 2 mg dose. These results, clearly indicate that 1 mg/day should be the highest recommended for monotherapy of early Parkinson's Disease.

- The sponsor did not submit the Statistical Analysis Plan for the placebo-controlled phase of

CLINICAL REVIEW

this study until after the Code/Blind was broken. The NDA notes that the Code/Blind was broken on 3/22/00 and the sponsor informed me that the Statistical Analysis Plan was then submitted to FDA/DNDP on that day. Despite the fact that our statisticians did not have seem to have an opportunity to review this analysis plan before breaking the blind, I do not necessarily view this as a critical problem of concern. It should be recognized that the protocol noted that covariates to be included in the analysis model were age, gender, baseline UPDRS, and previous use of selegiline and/or anti-cholinergics, but that the Statistical Analysis Plan only identified baseline UPDRS as the covariate to included in the model. Nevertheless, the principal statistical analysis (i.e. the baseline adjusted analysis of covariance) of the primary efficacy endpoint that was specified in the statistical analysis plan had been identified in the protocol and both documents noted that terms for treatment and center were to be incorporated in the analysis. Although it was not desirable to break the blind before DNDP statisticians had an opportunity to review the sponsor's Statistical Analysis Plan, I consider that the primary statistical analysis of the primary efficacy endpoint that was conducted was reasonable and valid for drawing conclusions about the efficacy of rasagiline in the placebo-controlled phase. I have discussed this issue with the statistical reviewer (Dr. Yan) and she is in agreement that the primary analysis of the primary efficacy endpoint is appropriate and valid.

- The sponsor did not make any adjustments for multiplicity with respect to assessing multiple, various analyses of the primary efficacy outcome measure and multiple analyses of many secondary efficacy endpoints. The sponsor's p values when presented were always nominal values. Despite the fact that multiple, various analyses of the placebo-controlled phase suggest various therapeutic effects of rasagiline, the sponsor's results of multiple analyses are best considered exploratory in nature and should not necessarily be viewed as indicative of a therapeutic benefit of rasagiline. Thus, I concur in this perspective of the statistical reviewer, Dr. Yan.
- The sponsor noted that the statistically significant differences for each of the rasagiline treatments (vs placebo) for the primary efficacy endpoint seemed to be driven by the ADL and motor subscale results. Thus, this beneficial treatment effect of rasagiline was mediated primarily by beneficial effects on ADL and motor function. Whereas, the unadjusted (i.e. not corrected for multiplicity) statistical analyses of these secondary efficacy endpoints (e.g. the UPDRS subscales) using LOCF imputation revealed highly significant nominal p values ($p < 0.0050$) for each rasagiline dose for ADL and motor function, the change for mental function (i.e. subscale I) was borderline significant ($p = 0.0503$) for 2 mg rasagiline and not significant ($p = 0.1771$) for 1 mg rasagiline. It is also interesting to note that changes in subscale scores for ADL and motor function from baseline to week 26 or termination visit were similar for analyses using LOCF imputation and actual visit data. Baseline changes of "total" UPDRS throughout the study were also fairly similar for LOCF imputation and actual data collected (Table 54 and Table 55). However, there appeared to be distinct, numerical treatment differences in the mean changes of mental function associated with each rasagiline dose (vs placebo) between week 4 and 26/termination visit when actual data collected at each visit were reviewed (Table 71). Such apparent treatment differences were not suggested based upon the LOCF analysis for mental function (Table 59). Although an explanation for this difference is not completely clear, I did note that the number of patients in each treatment

CLINICAL REVIEW

group in the actual data collected table (Table 71) did not change from baseline the study to the week 26/termination visit. The number of patients in each treatment group should have progressively decreased as patients dropped out and entered the active treatment phase as was observed in the corresponding tables for actual data collected for ADL and Motor scores. I have asked the sponsor to clarify this and have not yet received an explanation or answer as of 5/14/04. I agree that a therapeutic benefit of rasagiline clearly seems to be greater on the ADL and motor function subscales compared to mental subscale. However, I would not necessarily dismiss the possibility that rasagiline may also be capable of producing some therapeutic benefits on mental functioning if the sponsor is able to verify the accuracy of the more prominent changes from baseline described in the actual data collected table and suggesting a beneficial effect of rasagiline.

Active Treatment Phase

- The sponsor conducted a double-blinded, active treatment phase (up to 26 weeks) that followed the randomized, double-blind, placebo-controlled phase (up to 26 weeks) and that involved a delayed start of 2 mg/day rasagiline in patients previously treated with placebo in the first study phase. Patients who had been treated with 2 mg/day rasagiline for up to 12 months appeared to show a statistically significant lower change of "total" UPDRS (i.e. part I + II + III) from baseline than patients who had been treated with placebo for up to 26 weeks in the first phase and with rasagiline 2 mg/day for up to 26 weeks in the second, active treatment phase. The sponsor interpreted its analysis of "total" UPDRS change from baseline to the end of the active treatment phase as suggesting a delay in the progression of Parkinson's Disease by 2 mg/day rasagiline. It should be recalled that all efficacy data included in the analyses would have been collected without addition of any dopaminergic therapy or prior to the addition of any dopaminergic and carrying forward the last efficacy data collected before of such treatment. Although I would agree that the efficacy data collected are somewhat suggestive of a delay in the progression of Parkinson's Disease, I believe that there are many concerns with the design and analysis of this study that make these data at best, only suggestive of an effect of rasagiline on progression of Parkinson's Disease. Initially, I will present and discuss some additional efficacy analyses that I consider worth noting and then will comment on my concerns about the sponsor's study design and statistical analyses of the active treatment phase.
- In response to my request, the sponsor conducted additional analyses showing the effects of treatment on "total" UPDRS change from baseline and change from week 26 in patients who entered the active treatment phase and did not receive any additional dopaminergic in that phase. Thus, data collected from these patients in the active phase would be actual data collected and not efficacy data carried forward. There were 89, 82, and 91 such patients in the 1 mg, 2 mg, and placebo/2 mg groups respectively and almost all of these (86, 77, and 86 respectively) completed a full 52 weeks of study including 26 weeks in the placebo-controlled phase and 26 weeks in the active treatment phase. I have also conducted my own analyses of some of these subgroups of patients and shown their results including changes from baseline and from week 26 for "total" UPDRS and treatment effects of changes (i.e. mean 1 or 2 mg/day rasagiline change result at each post-treatment visit – mean placebo change result at

CLINICAL REVIEW

Table 71 Descriptive Statistics of UPDRS Mental Score at Baseline, Throughout Study, and Change from Baseline for Actual Data Collected

TVP-10120232 Placebo-Controlled Phase		Total UPDRS				Total UPDRS (Change)			
		1 MG	2 MG	PLACEBO	All	1 MG	2 MG	PLACEBO	All
Baseline	N	134	132	138	404	134	132	138	404
	Mean	24.69	25.89	24.54	25.03	0.00	0.00	0.00	0.00
	Std	11.25	9.54	11.61	10.84	0.00	0.00	0.00	0.00
	Min	5.50	10.50	5.50	5.50	0.00	0.00	0.00	0.00
	Max	75.00	53.50	61.00	75.00	0.00	0.00	0.00	0.00
Week 4	N	134	132	138	404	134	132	138	404
	Mean	23.68	24.47	24.29	24.15	-1.01	-1.41	-0.24	-0.88
	Std	11.59	10.31	12.14	11.36	4.57	4.34	5.47	4.84
	Min	3.50	3.50	5.50	3.50	-15.00	-11.50	-17.50	-17.50
	Max	75.50	53.00	83.00	83.00	11.00	9.50	22.00	22.00
Week 8	N	134	132	138	404	134	132	138	404
	Mean	23.18	24.63	25.65	24.50	-1.51	-1.25	1.12	-0.53
	Std	11.50	11.01	13.39	12.04	5.24	5.17	6.34	5.73
	Min	3.50	3.50	5.00	3.50	-31.00	-18.00	-12.50	-31.00
	Max	62.50	61.00	83.00	83.00	11.50	14.00	25.50	25.50
Week 14	N	134	132	138	404	134	132	138	404
	Mean	23.32	24.99	26.01	24.79	-1.37	-0.89	1.48	-0.24
	Std	11.31	10.98	13.59	12.06	5.75	5.35	6.49	6.01
	Min	3.50	1.00	5.00	1.00	-27.50	-11.50	-14.50	-27.50
	Max	61.50	56.00	83.00	83.00	12.00	12.00	22.00	22.00
Week 20	N	134	132	138	404	134	132	138	404
	Mean	24.04	25.64	27.28	25.67	-0.65	-0.24	2.75	0.64
	Std	12.27	11.49	14.05	12.70	6.32	5.81	6.99	6.56
	Min	3.50	3.00	6.50	3.00	-37.00	-14.50	-19.00	-37.00
	Max	75.00	58.00	83.00	83.00	15.00	16.00	24.00	24.00
26 Termination	N	134	132	138	404	134	132	138	404
	Mean	24.75	26.61	28.44	26.62	0.06	0.72	3.91	1.59
	Std	12.26	11.83	14.30	12.92	6.82	5.82	7.45	6.93
	Min	4.00	3.50	5.00	3.50	-39.00	-14.00	-18.50	-39.00
	Max	69.00	58.00	83.00	83.00	26.00	21.00	23.50	26.00

each respective post-treatment visit). These analyses provide a numerical estimate of the treatment effect of rasagiline and also show and compare changes not only from baseline but also relative to week 26 (beginning of the active treatment phase).

Table 72 shows “total” UPDRS scores, changes from baseline and from week 26 (beginning of active treatment phase) when patients treated with placebo in the placebo-controlled phase start the active treatment phase and receive 2 mg /day rasagiline for up to 26 weeks. These results show the impact of a delayed start of that dose compared to results of patients continually treated with 2 mg/day rasagiline for up to 26 weeks in each phase. Table 72 also shows a “treatment” effect of placebo for these changes by subtracting the mean placebo change result from the respective mean rasagiline change result. These data presented are for all patients who entered the active phase in each treatment group and had at least a single

CLINICAL REVIEW

efficacy assessment after week 26 for “total” UPDRS. Approximately one third of the patients in each group required additional dopaminergic medical therapy (e.g. LD or dopaminergic agonist) and therefore had their last efficacy assessment collected prior to the additional therapy carried forward up through 26 weeks after the initiation of the active treatment phase. Analyses of the treatment effect throughout the placebo-controlled phase (baseline – week 26) showed that the beneficial treatment effect (i.e. lower “total” UPDRS score compared to placebo) appeared at week 4, and gradually became numerically greater (i.e. more negative change) over the 26 weeks until reaching approximately -3, (i.e. indicating 3 points less change from baseline for “total” UPDRS). However, the treatment effect was similar for each dose of rasagiline. During the active treatment phase, the treatment effect (for change from baseline) decreases relative to the placebo-controlled phase and at the end of the active phase this treatment effect has narrowed to -1.16 for the 1 mg/day rasagiline group and to -2.20 for the 2 mg/day rasagiline group. These data suggest that patients treated with rasagiline for the full period of both phases exhibit better UPDRS performance and less disease progression than patients who started rasagiline 2 mg/day much later. The effect of 2 mg/day is nearly double that of the 1 mg/day group.

When one views these data with respect to changes from week 26 or termination visit of the placebo-controlled phase, it is apparent that there is a positive change in the “total” UPDRS for the 1 and 2 mg/day rasagiline groups. This positive change indicates that the group of patients who started 2 mg/day rasagiline (after previous placebo treatment) is showing better performance on UPDRS than patients who have been treated continuously with each dose of rasagiline since baseline (prior to the placebo-controlled phase). At the end of the active treatment phase, patients treated always with 1 mg/day showed nearly a positive increase of mean UPDRS score relative to the former placebo patients now treated with 2 mg/day. Patients treated with 2 mg/day always were only slightly worse than former placebo patients as manifested by a positive score increase of 1. Altogether these analyses show that the patients who received a delayed start of rasagiline treatment experienced similar therapeutic benefit and of a similar magnitude as patients had experienced in each rasagiline group at the end of placebo-controlled phase.

I was concerned that patients dropping out of the efficacy data collections to be included in the analyses via LOCF imputation might present a different picture of efficacy results than might be presented if one analyzed results of patients who participated in both phases of the study for the full 52 weeks (12 months) and who did not receive any additional “dopaminergic” therapy other than rasagiline. Thus, I analyzed the treatment effect (mean rasagiline change – mean placebo change) of patients who were participants of all 52 weeks of the study to explore the apparent effect of treatment over a full year. For these patients, Table 73 shows their results for “total” UPDRS, change from baseline and change from week 26/termination visit and Table 74 shows similar results for mean data and also treatment effects (rasagiline – placebo) for the changes from baseline and the changes from week 26/termination visit. When changes from baseline were compared for a treatment effect of rasagiline, the mean difference in “total” UPDRS was -1.72 points lower than that of patients who received a delayed start of 2 mg/day rasagiline by 6 months. This treatment difference was relatively similar in magnitude (-2.20) as that observed when all patients who enrolled in the active phase were considered and LOCF was employed for patients requiring

CLINICAL REVIEW

additional dopaminergic therapy (Table 73). However, the treatment difference almost disappeared (i.e. - 0.29) at the end of 52 weeks in patients who had received 1 mg/day rasagiline for the whole study (Table 74). The treatment differences at the end of the active treatment phase were comparable for each rasagiline group treated for 52 weeks for change from week 26/termination visit to those values observed in patients who did not receive treatment for all 52 weeks and who contributed efficacy data results based upon LOCF imputation. In summary, my supplementary, exploratory analyses support the view that 2 mg/day of rasagiline may exert a delay or slowing of progression of Parkinson's Disease. This hypothesis requires rigorous testing in future investigation.

Table 72 Efficacy Cohort : Descriptive Statistics of "Total" UPDRS and Change from Baseline During the Entire Study by Scheduled Visit for Enrollees of the Active Treatment Phase (LOCF in each phase)

Placebo-Controlled and Active Treatment Phases	"Total" UPDRS			"Total" UPDRS Change from Baseline						"Total" UPDRS Change from Wk 26 or Termination Visit			
	Treatment 1 mg N=122	2 mg N=119	Pl/ 2 mg N=130	1 mg N=122		2 mg N=119		Pl/ 2 mg N=130	1 mg N=122		2 mg N=119		Pl/ 2 mg N=130
Timepoint				Δ	Rx Eff Δ	Δ	Rx Eff Δ	Δ	Δ	Rx Eff Δ	Δ	Rx Eff Δ	Δ
Baseline Mean	24.45	25.12	23.85										
Week 4 Mean	23.40	23.26	23.48	-1.05	0.68	-1.86	1.49	0.37					
Week 8 Mean	22.91	23.51	24.80	-1.53	2.48	-1.61	2.59	0.95					
Week 14 Mean	23.07	23.89	25.08	-1.38	2.61	-1.23	2.46	1.23					
Week 20 Mean	23.94	24.54	26.34	-0.50	2.99	-0.58	3.07	2.49					
Week 26 /Termination Mean	24.54	25.63	27.56	0.09	-3.62	0.51	-3.20	3.71					
Week 32 Mean	24.36	25.22	26.16	-0.09	-2.40	0.10	-2.21	2.31	-0.18	1.22	-0.41	0.99	-1.40
Week 42 Mean	25.71	26.58	26.85	1.27	-1.73	1.46	-1.54	3.00	1.18	3.43	0.95	3.20	-2.25
Week 52 Mean	27.45	27.10	28.02	3.01	-1.16	1.97	-2.20	4.17	2.92	2.42	1.46	1.00	0.46

Δ Change from Baseline or Week 26

Δ Rx effect = Treatment Effect Change = Difference of (Δ result of 1 mg or 2 mg group - Δ Placebo/2 mg result)

CLINICAL REVIEW

Table 73 Descriptive Statistics of “Total” UPDRS and Change from Baseline and from Week 26 for Full 12 Month Completers of the Entire Study Without Additional Dopaminergic Therapy

TVP-1012/232 Tempo		Total UPDRS				Total UPDRS (Change from Baseline)				Total UPDRS (Change From Week 26)			
		1 mg	2 mg	Placebo/2 mg	All	1 mg	2 mg	Placebo/2 mg	All	1 mg	2 mg	Placebo/2 mg	All
Baseline Visit	N	89	82	91	262	0	0	0	0	0	0	0	0
	Mean	23.02	23.34	20.93	22.39
	Median	21.00	22.25	19.50	20.50
	Std	11.67	8.94	8.55	9.85
	Max	75.00	53.50	44.50	75.00
Week 4 Visit	N	89	82	91	262	89	82	91	262	0	0	0	0
	Mean	21.74	21.41	20.35	21.15	-1.28	-1.92	-0.58	-1.24
	Median	19.00	20.75	20.00	19.75	-1.50	-2.00	0.00	-1.00
	Std	12.02	8.83	8.76	9.99	4.28	3.30	5.24	4.40
	Max	75.50	49.50	53.00	75.50	10.00	8.00	12.50	12.50
Week 8 Visit	N	88	81	91	260	88	81	91	260	0	0	0	0
	Mean	21.11	21.85	21.53	21.49	-1.71	-1.35	0.60	-0.79
	Median	18.25	20.50	20.00	20.00	-2.00	-2.00	0.00	-1.00
	Std	11.52	10.20	10.35	10.68	5.53	4.73	6.04	5.56
	Max	62.50	61.00	70.00	70.00	11.50	14.00	25.50	25.50
Week 14 Visit	N	89	81	91	261	89	81	91	261	0	0	0	0
	Mean	21.02	21.83	21.63	21.48	-2.00	-1.64	0.69	-0.95
	Median	18.00	21.00	19.00	19.50	-1.00	-1.50	0.00	-1.00
	Std	11.05	9.30	10.23	10.21	5.98	4.66	6.35	5.85
	Max	61.50	52.00	57.00	61.50	12.00	10.50	21.00	21.00
Week 20 Visit	N	86	79	86	251	86	79	86	251	0	0	0	0
	Mean	22.08	21.85	22.03	21.99	-1.07	-1.59	1.07	-0.50
	Median	18.75	20.50	20.00	20.00	-1.25	-1.00	0.50	-1.00
	Std	12.55	10.23	10.25	11.05	6.76	5.25	6.76	6.41
	Max	75.00	57.00	53.50	75.00	15.00	13.50	24.00	24.00
Week 26 (Placebo Controlled Termination) Visit	N	87	78	86	251	87	78	86	251	0	0	0	0
	Mean	22.64	22.67	23.34	22.89	-0.51	-0.67	2.38	0.43
	Median	20.00	20.75	20.75	20.50	0.00	-1.00	2.00	0.00
	Std	11.97	10.70	10.64	11.10	7.00	5.22	7.36	6.76
	Max	60.00	58.00	52.50	60.00	13.50	14.50	23.50	23.50
Week 32 Visit	N	89	80	91	260	89	80	91	260	89	80	91	260
	Mean	21.56	22.16	21.66	21.78	-1.46	-1.05	0.73	-0.57	-0.83	-0.59	-1.95	-1.15
	Median	19.00	21.25	19.50	20.25	-1.50	-0.50	0.00	-0.50	-0.50	0.00	-1.50	-1.00
	Std	13.19	10.51	10.66	11.50	7.68	6.03	7.62	7.23	4.71	4.74	5.01	4.84
	Max	78.00	59.00	54.00	78.00	15.00	19.00	28.00	28.00	18.00	14.00	13.00	18.00
Week 42 Visit	N	88	82	91	261	88	82	91	261	88	82	91	261
	Mean	22.88	24.14	22.03	22.98	-0.13	0.80	1.10	0.59	0.53	1.19	-1.57	0.01
	Median	20.75	22.75	20.00	21.00	-0.50	0.50	1.00	0.50	0.50	1.00	-1.00	0.00
	Std	12.50	10.68	10.79	11.35	6.65	5.90	7.95	6.91	5.15	4.08	5.83	5.22
	Max	80.50	61.50	54.00	80.50	17.50	16.50	38.00	38.00	20.50	11.50	16.00	20.50
Week 52 (Active Phase Termination) Visit	N	89	82	91	262	89	82	91	262	89	82	91	262
	Mean	25.26	24.89	23.70	24.60	2.24	1.55	2.77	2.21	2.87	1.94	0.10	1.61
	Median	24.50	25.50	21.00	23.00	2.50	1.25	2.00	2.00	2.00	2.00	-0.50	1.50
	Std	14.22	11.05	12.40	12.63	8.76	6.86	9.14	8.45	6.42	5.20	7.45	6.54
	Max	70.00	58.50	61.00	70.00	27.50	22.50	45.00	45.00	31.00	15.00	24.00	31.00

CLINICAL REVIEW

Table 74 Descriptive Statistics of “Total” UPDRS and Change from Baseline and from Week 26 for Full 12 Month Completers of the Entire Study Without Additional Dopaminergic Therapy

Placebo-Controlled and Active Treatment Phases	“Total” UPDRS			“Total” UPDRS Change from Baseline					“Total” UPDRS Change from Wk 26 or Termination Visit				
	Treatment	1 mg N=86	2 mg N=77	Pl/ 2 mg N=86	1 mg N=86	2 mg N=77	Pl/ 2 mg N=86	1 mg N=86	2 mg N=77	Pl/ 2 mg N=86	1 mg N=86	2 mg N=77	Pl/ 2 mg N=86
Timepoint				Δ	Rx Eff Δ	Δ	Rx Eff Δ	Δ	Δ	Rx Eff Δ	Δ	Rx Eff Δ	Δ
Baseline Mean	23.13	23.42	20.96										
Week 4 Mean	22.01	21.51	20.10	-1.12	0.26	-1.91	1.05	0.86					
Week 8 Mean	21.32	21.67	20.98	-1.60	1.62	-1.60	1.62	0.02					
Week 14 Mean	21.26	21.69	21.25	-1.87	2.16	-1.73	2.02	0.29					
Week 20 Mean	22.16	21.61	22.03	-0.97	2.04	-1.79	2.86	1.07					
Week 26 /Termination Mean	22.59	22.68	23.34	-0.54	2.92	-0.75	3.13	2.38					
Week 32 Mean	21.84	22.19	21.58	-1.28	1.90	-1.09	1.70	0.62	-0.74	1.02	-0.25	1.51	-1.76
Week 42 Mean	23.12	23.79	22.05	-0.01	1.10	0.36	0.73	1.09	0.53	1.82	1.11	2.40	-1.29
Week 52 Mean	25.69	24.55	23.81	2.56	-0.29	1.13	-1.72	2.85	3.10	2.63	1.88	1.41	0.47

Δ Change from Baseline or Week 26

Δ Rx effect = Treatment Effect Change = Difference of (Δ result of 1 mg or 2 mg group - Δ Placebo/2 mg result)

- I have many concerns with the sponsor’s statistical analyses of the active treatment phase :
 1. The sponsor did not prospectively specify a primary efficacy endpoint for the active treatment phase. The protocol did not note that efficacy data would be analyzed in the active treatment phase but noted that this phase was included to collect additional safety data. The Statistical Analysis Plan (SAP) that described various efficacy assessments to be analyzed did not identify a single primary efficacy endpoint but instead described

CLINICAL REVIEW

several primary and secondary analyses of several efficacy endpoints and even noted that efficacy measures were being explored. Neither was there any specification that there would be any statistical corrections/adjustments for multiplicity.

2. I confirmed from the sponsor that the SAP was never submitted for review and feedback by DNDP statistical colleagues prior to breaking the blind of the active treatment phase. Thus, it is possible that the analyses proposed by the sponsor may have been influenced by the breaking the blind despite the fact that the finalization date of the SAP is the same as the date that the Code/Blind was broken.
 3. An analysis of change in median “total” UPDRS from baseline that was presented to show a statistically significant benefit of 2 mg/day rasagiline suggested a delay in disease progression was not an analysis prespecified in the SAP. In contrast, this application of a non-parametric analysis appeared to be a post-hoc analysis conducted after the sponsor reviewed and analyzed the data.
 4. Some efficacy outcome measures presented by the sponsor such as those dealing with changes in “total” UPDRS AUC were not even described in the SAP. In addition, other efficacy endpoints (e.g. need for LD, QOL, Clinical Global Impression, Timed Motor Tests) that were supposed to be analyzed according to the SAP were not presented. Presumably, analyses of the efficacy outcome measure not presented did not suggest a beneficial effect of treatment with rasagiline in both study phases on disease progression compared to rasagiline only in the active treatment phase.
 5. “Efficacy” suggesting delayed disease progression was based upon the analysis of the change from baseline of an efficacy assessment only at a single timepoint at the end of 26 weeks of active treatment (and involving LOCF when appropriate). A statistical analysis that analyzes data to show slopes that are statistically parallel and non-converging would seem to be important and provide a more robust analysis arguing for a therapeutic benefit of a delay in disease progression.
- I also have some comments or concerns about the study design used that I consider suboptimal for demonstrating a drug’s therapeutic benefit on disease progression :
 1. There was no randomization of patients immediately before initiating the active treatment phase. Randomization of patients only occurred at baseline prior to entering the placebo-controlled phase. It would have seemed better if :1) patients who had been treated with placebo prior to entering the active treatment phase would have been randomized 50 % to placebo and 50 % to 2 mg/day rasagiline; and 2) patients who had been treated with 2 mg /day rasagiline prior to entering the active treatment phase would have been randomized 50 % to placebo and 50 % to 2 mg/day rasagiline.
 2. It also seems possible that the fact that everyone knew that active treatment was being provided in the second 26 week treatment phase could have increased the “noise” in the system affecting the UPDRS scores because of the expectation of therapeutic benefit when you know “active” drug is being used.

CLINICAL REVIEW

3. The sponsor did not conduct any follow-up analysis to show what happened to “total” UPDRS scores after treatment is stopped. This was not done because the protocol was amended to delete the follow-up visit 6 weeks after the last treatment so that patients would enter an open-label safety trial. It would have been interesting to see what happens to these efficacy endpoints after all treatments were discontinued.

11.1.5. Reviewer’s Conclusions

- Rasagiline showed a robust therapeutic effect on the primary efficacy outcome measure, change of “total” UPDRS (i.e. sum of parts I-Mental + II-ADL + III-Motor) from baseline to termination (up to 26 weeks) of the placebo-controlled phase and indicates that rasagiline is effective as monotherapy in “early” patients with Parkinson's Disease who are not taking concomitant dopaminergic therapy.
- Both doses (1 and 2 mg/day) of rasagiline were therapeutically effective and 2 mg/day did not suggest any additional therapeutic over that produced by 1 mg/day.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- Although the sponsor’s analyses showed nominally statistically significant, beneficial effects of rasagiline on multiple secondary efficacy endpoint in both study phases, I cannot draw serious conclusions about the efficacy on these endpoints because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons.
- Based upon exploratory analyses, rasagiline “monotherapy” may have the potential to exert a beneficial effect on slowing/delaying disease progression of patients with “early” Parkinson's Disease but this effect should be investigated in studies that are carefully, and appropriately designed and statistically analyzed.

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CLINICAL REVIEW

11.2. Study TVP-1012/133 PRESTO (Study Showing Efficacy)

11.2.1. Description of Protocol TVP-1012/133 PRESTO (Study Showing Efficacy)

Title of Study : TVP-1012/133 (PRESTO) - A Multicenter, US and Canada, Double Blind, Randomized, Placebo-Controlled, Parallel Group Study, for the Efficacy, Tolerability and Safety of Rasagiline Mesylate in Levodopa (LD) Treated Parkinson's Disease Patients with Motor Fluctuations.

Study initiation date : 12/4/00

Study completion date : 1/14/03

Protocol Description

Objectives :

To evaluate the efficacy, tolerability and safety of 2 dosages of rasagiline compared to placebo in PD subjects with motor fluctuations on levodopa (LD) therapy.

Primary Efficacy Endpoint – change from baseline in the mean total daily “OFF” time, as measured by home diaries.

Secondary Efficacy Endpoints

- Change in UPDRS, Part III (Motor) during “ON” state.
- Change in UPDRS, Part II (Activities of Daily Living, ADL) during “ON” state.
- Change in UPDRS, Part II (ADL) during “OFF” state.

Safety

- Adverse event frequency and severity, changes in vital signs and clinical laboratory values.
- Change in duration of “ON with troublesome dyskinesia” time as measured by home diaries.
- Change in UPDRS, Part I (Mental).
- Number of subjects with post prandial increases in systolic blood pressure of more than 30 mmHg, on one or more occasions, as recorded during home blood pressure monitoring (Appendix XIV).

Tolerability

CLINICAL REVIEW

- Number of subjects who discontinue the study
- Number of subjects who discontinue the study due to adverse events.

Pharmacokinetics / Pharmacodynamics

- Population pharmacokinetics (PK) by rasagiline and AI blood levels
- Pharmacodynamic measurement by platelet MAO-B activity sub study

Exploratory Efficacy Endpoints

- Change in Clinical Global Evaluation scale rated by subjects and investigators.
- Change in the Schwab and England ADL scale rated by subjects and investigators at “ON” and “OFF” state.
- Change in levodopa dosage.
- Change in a Quality of Life scale (PD QUALIF).

STUDY DESIGN and SCHEDULE :

This was a multi-center, double-blind, randomized, placebo-controlled study in parallel groups of PD subjects with motor fluctuations on levodopa therapy. About 450 subjects were to be randomized equally to one of 2 dosages of rasagiline (0.5 mg and 1 mg) or placebo. Subjects withdrawing from the trial before completion were not to be replaced.

Following a screening visit to ensure that subjects met all enrollment criteria and could accurately complete home diaries, subjects were to be randomized to one of 2 dosages of rasagiline or matching placebo. LD dosage could be decreased for the first 6 weeks of the study period at the discretion of the investigator, in the event of intolerability and was supposed to remain constant for the last 20 weeks. Subjects were to have visits at 3, 6, 10, 14, 20, and 26 weeks after baseline for safety and efficacy monitoring. A home diary in which subjects rate themselves as “ON without dyskinesias or ON without troublesome dyskinesias”, “ON with troublesome dyskinesias”, “OFF”, or “asleep” every half hour was to be completed for 3 days immediately prior to Baseline, Weeks 6, 14, and 26. Subjects were to monitor blood pressures before and after the main meal of the day for 7 days prior to Baseline, Weeks 3, and 26. The study was to last 6 months to allow evaluation of long-term efficacy and safety.

Results from a phase III monotherapy study showed that rasagiline 1 mg/ day was as efficacious as 2 mg/day. This study was to investigate the efficacy of 1 mg rasagiline as adjunct therapy to LD. A lower dose, 0.5 mg, was to be tested as well. The dosages selected had been shown to be well tolerated in previous studies.

Rasagiline may increase the effect of tyramine (a substance found in some foods, primarily aged

CLINICAL REVIEW

cheeses and wines). Tyramine can lead to transient, post-prandial increase in blood pressure, which may cause headache, confusion or chest pain. In the studies conducted so far, rasagiline 1 mg/day did not show more interaction with tyramine than placebo. The sponsor noted that patients taking rasagiline 1 mg/day have not experienced any hemodynamic changes following large doses of tyramine (up to 75 mg) given before or after food. The following was reported with rasagiline 2 mg/day:

- In a study where rasagiline was given with LD, 2 subjects experienced elevated blood pressure readings after taking a high dosage (up to 75 mg) of tyramine, before food. Both subjects were taking rasagiline 2 mg daily and LD.
- In another study, two subjects, also on 2 mg/day rasagiline, had a modest increase in their blood pressure after taking a high dosage (75 mg) of tyramine half an hour after food. These subjects had been taking only rasagiline for their Parkinson's disease.

To determine whether the rasagiline dosages used in this study could cause asymptomatic changes in blood pressure while on an unrestricted diet, subjects were to monitor their blood pressures at home before and after the main meal of the day, for a period of one week before baseline, before the Week 3 visit, and before the Week 26 (Termination) visit.

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CLINICAL REVIEW

Figure 32 Schedule of Assessments / Events

	Double Blind Phase							
	Screening	Levodopa Dosage Adjustment			Maintenance Phase			Termination
			Baseline	week 3	week 6	week 10	week 14	week 20
Day	-28 to -10		+/- 5	+/- 5	+/- 5	+/- 5	+/- 7	+/- 7
Visit #	SC	00	01	02	03	04	05	06
Informed consent	X							
Inclusion/Exclusion Criteria	X	X (review)						
Medical History	X	X (review)						
Physical/Neurological Exam	X							X
PD QUALIF		X						X
Hoehn & Yahr	X							
SE ADL		X						X
MMSE	X							
Beck Depression	X							
Chest X-ray ¹	X ¹							
ECG	X							X
Pregnancy Test ²	X ²							X ²
Vital Signs	X	X	X	X	X	X	X	X
Diary Training	X							
Review Home Diaries (to be completed for 3 days prior to visit)		X		X		X		X
Home Blood Pressure Monitoring ³		X ³	X ³					X ³
UPDRS I, III, IV - "on" II - "ON and OFF")		X			X			X
Clinical Global Evaluation		X						X
Concomitant Therapy	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X
Call to CTCC for Randomization		X						
Dispense Study Medication		X	X	X	X	X	X	
Retrieve Study Medication			X	X	X	X	X	X
Safety Laboratory Tests	X	X			X			X
PK Laboratory Studies					X			X
MAO-B ⁴		X ⁴			X ⁴			X ⁴
Investigator's Signature	X	X	X	X	X	X	X	X
Study Termination								X
Subject Disposition		X						
AE follow up								X

1. CXR if not completed in last 6 months
2. For women of child-bearing age only.

3. To be completed for 7 consecutive days prior to the visit and diary completion
4. Sub study #1 selected sites

Inclusion Criteria :

Subjects must meet all the inclusion criteria to be eligible :

1. Men and women with idiopathic Parkinson's disease whose diagnosis is confirmed by at least two of the cardinal signs (resting tremor, bradykinesia, rigidity) being present, without any other known or suspected cause of parkinsonism.
2. Subjects must experience levodopa related motor fluctuations averaging at least 2.5 hours daily in the "OFF" state, confirmed by the baseline home diaries.
3. Modified Hoehn and Yah stage < 5 in the "OFF" state.
4. Subjects must be taking optimized carbidopa/LD therapy (based on investigator's

CLINICAL REVIEW

judgment), stable for at least 14 days prior to baseline. Subjects must be receiving at least 3 daily doses of levodopa, not including a bedtime dose.

5. Subjects who are treated with entacapone should be on stable doses for at least 14 days prior to baseline. The dosage of entacapone should only be changed during the study period if the number of levodopa doses changes.
6. Subjects who are treated with dopamine agonists and other anti PD drugs should be on stable doses for at least 30 days prior to baseline. The dosage of dopamine agonists and other anti-PD drugs should remain constant throughout the study period.
7. Selegiline must be discontinued for at least 90 days prior to baseline.
8. Women must be postmenopausal, surgically sterilized, or using adequate birth control. Woman of childbearing potential must have a negative pregnancy test (serum beta-HCG) at screening.
9. Subject must be age 30 or older.
10. Subjects must be withdrawn from tolcapone and antidepressants, including selective serotonin reuptake inhibitors, tricyclic, and tetracyclic antidepressants (except amitriptyline, trazodone, citalopram, paroxetine, sertraline, and mirtazipine at stable low dosages) at least 42 days prior to baseline.
11. Subjects must be withdrawn from sympathomimetics (including over the counter (OTC) cold remedies - nasal or oral), dextromethorphan, pethidine, St. John's Wort and gentamicin, at least 7 days prior to baseline.
12. Subjects must demonstrate the ability to keep accurate diaries of activity prior to randomization; i.e. at least 75% concordance between subject and investigator/coordinator diary ratings must be achieved during the diary training session. Subjects must have at least one transition from "OFF" to "ON" or from "ON" to "OFF" during the training session. Subjects must be willing and able to complete adequate diaries throughout the study period.
13. Subjects must be willing and able to give informed consent.

Exclusion Criteria :

Any of the following will exclude the subject from the study :

1. Subjects with a clinically significant or unstable medical or surgical condition which would preclude safe and complete study participation. Such conditions may include cardiovascular, pulmonary, hepatic, renal, or metabolic diseases or malignancies as determined by medical history, physical exam, laboratory tests, chest x-ray, or ECG.

CLINICAL REVIEW

2. Subjects with clinically significant or unstable vascular disease, e.g.:
 - clinically significant arrhythmia or valvular heart disease as judged by investigator.
 - congestive heart failure (New York Heart Association class 2 or greater clinically significant arrhythmia or valvular heart disease as judged by investigator.
 - significant ischemic heart or cerebrovascular disease (such as unstable angina pectoris, stroke or myocardial infarction within the last 6 months.
 - severe hypertension (including after meals as noted on home blood pressure monitoring).
 - clinically significant orthostatic hypotension (and/or SBP change > 30mmHg).
 - clinically significant syncope associated with hypotension within the past 2 years.
3. Subjects with significant cognitive impairment as defined by MMSE score < 24.
4. Subjects with clinically significant psychiatric illness, including depression, (Beck (short form) depression scale > 15), which compromises their ability to provide consent or participate fully in the study.
5. Concomitant therapy with MAO inhibitors, reserpine, methyldopa within the past three months, or treatment with an anti-emetic or neuroleptic medication with central dopamine antagonist activity within the past six months.
6. Subjects with a history of alcohol or substance abuse within the past 2 years.
7. Subjects who have taken experimental medications within 60 days prior to baseline.
8. Subject who have undergone a neurosurgical intervention for Parkinson's disease (e.g., pallidotomy, thalamotomy, transplantation and deep brain stimulation).
9. Subjects with severe disabling dyskinesias.
10. Subjects with known serious adverse reaction to selegiline.
11. Subjects with known adverse reactions associated with ingestion of tyramine- containing food.
12. Participation in a previous clinical trial of rasagiline.

Efficacy Variables

Primary Efficacy Endpoint

The primary efficacy variable/endpoint was to be the change in the "OFF" time (derived from patient diaries) from baseline to the end of the study at week 26 or at the termination visit.

CLINICAL REVIEW

Secondary Efficacy Endpoints

- Change in UPDRS, Part III (Motor) during “ON” state.
- Change in UPDRS, Part II (Activities of Daily Living, ADL) during “ON” state.
- Change in UPDRS, Part II (ADL) during “OFF” state.

Exploratory Efficacy Endpoints

- Change in Clinical Global Evaluation scale rated by subjects and investigators.
- Change in the Schwab and England ADL scale rated by subjects and investigators at “ON” and “OFF” state.
- Change in levodopa dosage.
- Change in a Quality of Life scale (PD QUALIF).
- Subject Diaries - 24-hour diaries were to be completed for 3 days immediately prior to the designated visits. Subjects were supposed to rate their state, every 30 minutes, as "ON without dyskinesias or ON without troublesome dyskinesias", "ON with troublesome dyskinesias", "OFF", or "asleep". These ratings were to be used to determine mean total daily “OFF” time (the primary endpoint of the study), as well as the change in duration of time "ON with troublesome dyskinesias" (a secondary safety endpoint). The change in the “OFF” time was the primary outcome measure.
- Subjects were to be trained on diary completion at the Screening Visit. A practice diary was to be completed between Screening and Baseline, and this diary was to be reviewed by the site coordinator to ensure that the subject was capable of accurately filling out the diaries.
- UPDRS (parts I, II, III, IV) : UPDRS parts I to IV were to be completed. Part I and III (mental and motor sections) were to be completed in the "ON" state at the visits. The UPDRS Part II (ADL section) was to be completed in both the “ON” and “OFF” states at these visits. These scales were supposed to be completed by the same investigator at all visits. Parts II and III were secondary efficacy outcome measures. Part I was a safety outcome measure.
- Schwab England ADL scale : This scale was to be completed in both the “ON” and "OFF" state by the investigator and subject. The scale assesses the ability to perform ADLs, and was rated as a percentage in 5 % increments.

CLINICAL REVIEW

- PD QUALIF –The PD QUALIF was a disease specific Health Related Quality of Life (HQOL) instrument developed by the Quality of Life task force of the Parkinson Study Group. It has a 33 item questionnaire, that contains four domains: general health perception, psychological distress/well being, social and role functioning and physical function. Four individuals sub-scales and one total quality of life score would be evaluated.
- Clinical Global Evaluation : This scale was to be completed by the investigator and subject. The scale rates the subject's overall well being, including the Parkinson's disease symptoms over the week before the visit.

Compliance

- Study Drug Compliance - At each study visit the Investigator and/or site coordinator was to assess the subject's compliance with the prescribed regimen for the study medication. This evaluation was to include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who failed to comply with the study requirements could have been withdrawn from the study, following consultation with the sponsor.
- Subject Diary Compliance - 80% of the day was supposed to be filled in correctly in each of the 3-day diaries (fewer than ten missing or erroneous half-hour segments).

Safety and Pharmacokinetic Data were also to be collected. Details regarding the collection and analyses of these outcome measures can be found in the Clinical Safety Review of Dr. Lisa Jones and in the Biopharmaceutical Review of Dr. Andre Jackson.

Concomitant Medications

All concomitant medication that the subject was taking at study initiation were to be recorded on the concomitant medications log. In addition, any changes in concomitant medication or new medications added, including as a result of an intercurrent illness, was to be recorded in the case report forms.

Prohibited Medications

Subjects were not to receive concomitant therapy with any of the following:

- Other investigational therapy (washout period 60 days prior to study entry)
- Selegiline (washout period: 90 days prior to baseline)
- Tolcapone, at least 42 days prior to baseline
- Antidepressants, including selective serotonin reuptake inhibitors, tricyclic, and tetracyclic antidepressants (except amitryptiline [< 50 mg/day], trazodone [< 100

CLINICAL REVIEW

mg/day], citalopram [< 20 mg/day], paroxetine [< 30 mg/day], sertraline [< 100 mg/day], and mirtazipine [< 15 mg/day] at stable low dosages), at least 42 days prior to baseline.

- Sympathomimetics (including over the counter (OTC) cold remedies – nasal or oral), and dextromethorphan, at least 7 days prior to baseline.
- St. John's Wort, at least 7 days prior to baseline
- Meperidine, at least 7 days prior to baseline
- Gentamicin, at least 7 days prior to baseline

Anti-Parkinson Medication

- Levodopa-LD/carbidopa and entacapone treatment must be maintained at optimal and stable dosages (based on investigator's judgment) for 14 days prior to baseline.
- Subjects must be receiving at least 3 daily doses of LD, not including a bedtime dose. Subjects who are treated with dopamine agonists and other anti-Parkinson medications should be on stable dosages for at least 30 days prior to baseline and during the entire study period.

Dosage Adjustment

Dosages of LD could have been decreased at the discretion of the Investigator, in the event of intolerability, during the first 6 weeks of the study only. This dose reduction may have been accomplished by decreasing the amount of LD given per dose, by omitting a dose, or by increasing the interval between doses. If decreasing the dosage of LD led to a suboptimal response, the dosage could have been increased back to the baseline dosage (during the first 6 weeks of the study only), but should not have been increased above the baseline dosage. The dosage of entacapone should have been changed only if the number of LD doses changed and only during the first 6 weeks of the study. Dosages of other anti-Parkinson medications should not have been changed during the study period.

Planned Statistical Analyses (Statistical Methodology)

Sample Size Rationale

The power calculations were based on the primary endpoint: the change from baseline in the mean total daily "OFF" time, as measured through patient daily diaries at baseline and during treatment. The power was estimated under the assumption that the pooled standard deviation (SD) of the change from baseline of the mean total daily "OFF" time is 2.0 hours, estimated from Parkinson's Study Group (PSG) study with entacapone (Ann Neurol 1997;42;747-755).

The statistical test used was the t-test comparing the 0.5 mg group to placebo and the 1 mg group to placebo using Hochberg's Step-up Bonferroni procedure for multiple comparisons, with an overall ("experiment-wise") two sided alpha level of 0.05. Results of these calculations showed,

CLINICAL REVIEW

that a total of 450 patients, equally randomized to the three treatment groups would provide adequate power to detect (at 5 % significance level) a statistically significant difference between at least one of the rasagiline groups and the placebo group of > 45 minutes. The estimated power was calculated to lie between 84% and 94% when the true effect of the 1 mg dose compared to placebo is 45 minutes and the true effect of the 0.5 mg dose compared to placebo is between 0 minutes and 45 minutes. To examine whether the variance estimate that was used in the above sample size calculations was adequate, an assessment of the variance magnitude was to be performed after 1/3 of the patients had completed 26 weeks of treatment. The EM algorithm of Gould and Shih (Communications in Statistics. A Theory and Methods, 21, 2833-2853, 1992), was to be applied to estimate the pooled variance of the change from baseline in the mean total daily "OFF" time, without breaking the blind. In the case that the variance estimate was found to be larger than the one projected, the sponsor reserved the right to up-size the study via protocol amendment.

Randomization Procedures

After a subject met eligibility criteria, he/she would be allocated to one of the 3 treatment groups based on a randomization scheme with blocks stratified by centers. The randomization scheme was to be prepared by the Parkinson Study Group (PSG) using the SAS random number procedure. The randomization list and the seed used to generate the randomization list was to be kept sealed in a fire protected safe.

Subject Cohorts

The following subject cohorts were to be used in this study :

Intent-to-treat Cohort (ITT): Consists of all subjects randomized. In accordance with the ITT principle, all subjects randomized and who took at least one dose of the study drug will be kept in their originally assigned treatment group. This cohort will serve as the principal cohort for statistical inference.

Completers Cohort (CO): Consists of all subjects who completed the 26 weeks of the double-blind treatment.

Per Protocol Cohort (PP): Consists of all subjects who completed the 26 weeks of the double-blind treatment and did not have major protocol violations.

In the ITT cohort, the Last Observation Carried Forward (LOCF) approach was to be applied to account for missing data at study termination, for subjects with at least one post randomization evaluation. A subject who dropped out before the first post randomization evaluation, would be omitted from the efficacy analyses.

Safety assessment was to be performed on the ITT subject cohort only.

Significance Level

The significance level for this study was to be 5 % two-tailed. The treatment effect of rasagiline

CLINICAL REVIEW

was to be tested for significance by performing two comparisons for each end-point: the group treated with 1 mg/day was to be compared to placebo and the group treated with 0.5 mg/day was also to be compared to placebo. Hochberg's Step-up Bonferroni method was to be used to maintain the experiment-wise type I error of 5 %.

Comparability of Study Groups at Baseline

The last data recorded prior to randomization was to be considered as baseline data. The three treatment groups were to be compared for baseline characteristics. This analysis was to include demographic data, general medical history, clinical examinations taken prior to trial drug initiation, baseline laboratory data and baseline Parkinson's disease history. The continuous variables were to be examined using the one-way analysis of variance or the Kruskal-Wallis test when appropriate and the categorical variables were to be examined for differences between groups using the Chi-Square test or the Fisher's Exact test when appropriate.

Dropout (Drug Tolerability) Assessment

Drug tolerability analysis was to compare between the treatment groups the number (%) of subjects who failed to complete the study and the number (%) of subjects who failed to complete the study because of Adverse Events (AEs). Time to withdrawal was also to be assessed and presented by Kaplan-Meier curves and was to be compared using the Log-Rank test.

Efficacy Assessments

Efficacy assessment was to be performed on the ITT, CO and PP subject cohorts.

Primary Efficacy Endpoint : Change from baseline in the mean total daily "OFF" time, during treatment. The mean total daily "OFF" time was to be measured through 3 subject daily diaries prior to randomization (baseline measurement), and 9 subject daily diaries during treatment: 3 diaries prior to week 6, 3 diaries prior to week 14, and 3 diaries prior to week 26 (termination). The evaluation of the mean total daily "OFF" time during treatment was to be based on averaging measurements from week 6 through week 26 (9 daily diaries). The change between the mean value of the during treatment period to the mean value of the baseline period was defined as the change from baseline of the mean total daily "OFF", during treatment.

Principal Statistical Analysis

The principal statistical analysis of the primary endpoint will be an Analysis of Covariance (ANCOVA) accounting for baseline mean total daily "OFF" time. The adjusted means of the changes observed in each of the active drug groups (two comparisons) was to be compared versus placebo by applying an ANCOVA model (SAS GLM procedure) on the primary endpoint as dependent variable. The model was to include the following effects: treatment group, center, treatment-by-center interaction and baseline mean total daily "OFF" time. The treatment-by-center interaction was to be removed from the model if it was not statistically significant (i.e. if $p > 0.05$). The significance level for this analysis will be 5 %. Hochberg's Step-up Bonferroni method was to be used to maintain the experiment-wise type I error of 5 %.

CLINICAL REVIEW

The statistical model mentioned above assumed that there was no time effect on the primary efficacy endpoint. Although this assumption may be clinically justified, a test of a significant time effect was to be performed by applying a repeated measures analysis of covariance on the primary endpoint. The SAS MIXED procedure was to be used to elucidate the mechanism and the time course of the drug effect assuming that there is one. The model was to include, in addition to the effects of the principal model, the following effects: week in trial and treatment by week interaction. Statistical significance testing was to be conducted using the $-2 \log$ likelihood ratio test.

In addition the following complementary analyses were to be performed :

Change from baseline of the mean total daily "OFF" time, at termination visit

The analysis of the primary efficacy variable was to be repeated for termination versus baseline total daily "OFF" measurements. The evaluation of the change from baseline of the mean total daily "OFF" time, at termination visit was to be based on averaging the measurements from the 3 baseline diaries and measurements from the 3 diaries at termination visit only.

Categorical change from baseline of mean total daily "OFF" time (Responders Analysis)

The change from baseline of the mean total daily "OFF" time during treatment was to be dichotomized according to the cut-off point of an improvement of > 60 minutes. Baseline adjusted Logistic Regression (SAS GENMOD procedure) incorporating baseline mean total daily "OFF" time as a covariate, was to be performed to compare between the 2 active treatment groups and the placebo group. The model was to include the following effects : treatment group, center, treatment-by-center interaction and baseline mean total daily "OFF" time. The treatment-by-center interaction was to be removed from the model if it was not statistically significant (i.e. if $p > 0.05$ on the $-2 \log$ likelihood ratio test).

Secondary Efficacy Endpoints

Change from baseline UPDRS Motor during "ON" state

A secondary efficacy end-point for this study was the change in UPDRS Motor during "On" state from baseline to termination visit.

The baseline adjusted analysis of covariance (SAS PROC GLM) was to be used for comparing the adjusted means of the changes observed in each of the active drug groups versus placebo (two comparisons) incorporating terms for treatment and center. Baseline UPDRS Motor was to be included in the model as a covariate. The treatment-by-center interaction term was not to be included in the model if it was not statistically significant (i.e. if $p > 0.05$).

Change from baseline in UPDRS ADL (Activities of Daily Living) during "OFF" and "ON" state

An additional secondary efficacy end-point for this study was the change in UPDRS ADL (during "OFF" and "ON" states separately) from baseline to termination visit.

This analysis was to be similar to the UPDRS Motor analysis described above using baseline

CLINICAL REVIEW

UPDRS ADL rather than baseline UPDRS Motor as a covariate.

Exploratory Endpoints

Change from baseline in Clinical Global Evaluation Scale (CGE)

The CGE scale includes 2 sub-scales:

- Severity of Illness (Ranges from 0 = "Normal", to 6 = "Extremely ill")
- Global Improvement (Ranges from -3 = "Very much improved", though 0 = "No change", to 3 = "Very much worse")

The change from baseline to the termination visit of severity of illness was to be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by center.

The global improvement score was to be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by center.

Change from Baseline in PD-Qualif Scale

The change from baseline to termination in the PD-Qualif Scale was to be analyzed in the same way as the UPDRS Motor scale.

Change from baseline in Schwab and England ADL score

The change from baseline to termination in the Schwab and England ADL score (4 scales: rater and subject at "ON" and at "OFF" state) score was to be analyzed in the same way as the UPDRS Motor scale

Change from Baseline in Total Daily LD Dose

The change from baseline to termination in the total daily LD dose was to be analyzed using the baseline adjusted analysis of covariance (SAS PROC GLM). The adjusted means for change in each of the 2 active treatment groups (1 mg and 2 mg/day) were to be compared versus placebo (i.e. two comparisons). The model was to include terms for treatment and center effects and also baseline total daily LD dose and baseline total number of daily LD doses as covariates. The treatment-by-center interaction term was not to be included in the model if it was not statistically significant (i.e. if $p > 0.05$).

SAS software was to be used for statistical analysis and data presentation of the information collected in this study.

Summary of Significant Protocol Amendments

Amendment No.1 : 9/12/00

- There was an addition of another post prandial blood pressure measurement. Patients were to monitor blood pressures before and 45 minutes and 90 minutes after the main meal of the day instead of only 1 hour after a meal.

CLINICAL REVIEW

- All home monitored blood pressure readings transferred electronically were to be reviewed for excessively high values (systolic > 180 mm Hg or > 30 mm Hg increase from pre-prandial values).

Amendment No.2 : 9/2/01

- Modified exclusion criterion to allow enrollment of patients who had undergone neurosurgical intervention for Parkinson's disease (e.g., pallidotomy, thalamotomy, transplantation and deep brain stimulation) at least 12 months prior to baseline visit. Previously all such patients were not allowed.
- Allowed patients to enroll if clozapine or fumarate dose had been stable for at least 6 months prior to baseline.

11.2.2. Sponsor's Presentation of Results of Study TVP-1012/133 PRESTO

Most of the descriptions, summaries, tables, and figures presented here were taken from the sponsor's electronic submission.

Patient Disposition

The remaining 472 subjects underwent randomization. A total of 164 subjects entered the 0.5 mg/day rasagiline treatment group, 149 subjects entered the 1 mg/day rasagiline treatment group, and 159 subjects entered the placebo treatment group (Table 75). From the 0.5 mg/day rasagiline treatment group 142 subjects (87%) completed the full duration of the study and 22 subjects prematurely withdrew from the study. From the 1 mg/day rasagiline treatment group 132 subjects (89%) completed the study and 17 subjects prematurely withdrew from the study. From the placebo treatment group 140 subjects (88%) completed the study and 19 subjects prematurely withdrew from the study (Table 75).

Table 75 Patient Disposition

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Randomized	164	100.0	149	100.0	159	100.0	472	100.0
Prematurely Terminated the Study	22	13.4	17	11.4	19	11.9	58	12.3
Completed the Study	142	86.6	132	88.6	140	88.1	414	87.7

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2.1

The most common reason for prematurely withdrawing from the study was the experiencing of AEs with an overall incidence of 7% (Table 76). The 0.5 mg/day rasagiline treatment group had the largest withdrawal due to AEs (9%). This was followed by the 1 mg/day rasagiline treatment group (6%) and then by the placebo treatment group (5%). Premature withdrawals due to AE did not seem to be dose-related, and therefore the higher frequency in rasagiline-treated groups relative to the placebo treatment group may not be drug related.

CLINICAL REVIEW

Premature withdrawal due to the worsening of PD symptoms occurred with the highest incidence in the placebo treatment group (4%) compared to an incidence of approximately 1% in each of the rasagiline treatment groups. The withdrawal of subject consent occurred with an incidence of approximately 2% in each treatment group.

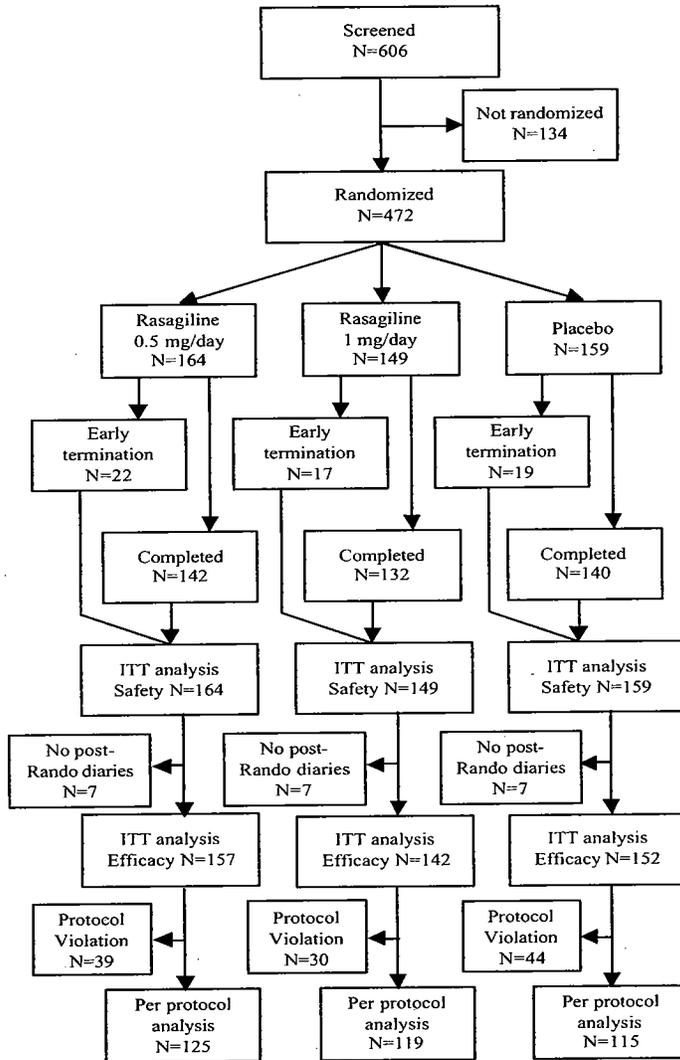
Table 76 Distribution of Termination Reasons

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Completion According to Protocol	142	86.6	132	88.6	140	88.1	414	87.7
Adverse Experiences	15	9.1	9	6.0	8	5.0	32	6.8
Lost to follow-up	0	0	0	0	0	0	0	0
Subject Withdrew Consent	3	1.8	3	2.0	3	1.9	9	1.9
Investigator's Decision	1	0.6	2	1.3	.	.	3	0.6
Sponsor's Decision	0	0	0	0	0	0	0	0
Initiation of exclusionary treatment	0	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0	0
Death	1	0.6	1	0.7	.	.	2	0.4
Other	.	.	1	0.7	1	0.6	2	0.4
Worsening of PD	2	1.2	1	0.7	7	4.4	10	2.1
All	164	100.0	149	100.0	159	100.0	472	100.0

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2.1

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Figure 33 Flow Diagram Depicting Progress of Subjects through the Study



Study Conduct and Major Protocol Deviations

On the whole, both patients and investigators complied well with study requirements and the study was well conducted.

Study Diaries

CLINICAL REVIEW

Approximately 99 % of diaries in each treatment group were considered to meet the definition of acceptable and were not considered unacceptable (i.e., had more than 5 missing or erroneous entries, not taking into account the half-hour time periods between 12 midnight and 6 a.m).

Study Drug Compliance

Out of 164 patients in the 0.5 mg/day rasagiline treatment group only 2 patients had a rasagiline compliance of less than 70%. Out of 149 patients in the 1 mg/day rasagiline treatment group only one patient had a rasagiline compliance of less than 70%. Out of 159 patients in the placebo treatment group only one patient had a placebo compliance of less than 70.

Protocol Deviations

The major deviations from the protocol that excluded subjects from the Per Protocol analysis are shown in Table 77. A total of 113 subjects were excluded from the PP cohort: in the rasagiline 0.5 mg/day and rasagiline 1 mg/day treatment groups there were 39 patients (24%), and 30 patients (20%) respectively compared to 44 patients (28%) in the placebo treatment group with major protocol violations.

The most common reason for exclusion from the Per Protocol cohort was premature termination from the trial. This was followed by having less than 6 acceptable treatment “24-hour” diaries which was mostly common in patients who terminated the trial early: 20 patients (12%) from rasagiline 0.5 mg/day treatment group, 12 patients (6%) from rasagiline 1 mg/day treatment group and 16 patients (10%) from placebo treatment group.

Table 77 Major Protocol Deviations

TVP-1012/133 (PRESTO)	0.5 mg (N=164)		1 mg (N=149)		Placebo (N=159)	
	N	%	N	%	N	%
Description						
Addition of New Anti-PD Medication or Stop of Existing Anti-PD Medication Post Randomization	7	4.26	3	2.01	3	1.88
Change in DA or Other anti-PD Medications Within Less than 30 Days Prior to Randomization	.	.	3	2.01	3	1.88
Increase or Decrease of more than 20% in the Dose of an Existing Anti-PD Medication	5	3.04	5	3.35	8	5.03
Increase or Decrease of more than 20% in the Mean Total Daily LD Dose During Treatment Period After Visit 2	6	3.65	7	4.69	5	3.14
Less than 2 Acceptable Diaries at Baseline	1	0.60
Less than 6 Acceptable Diaries During Treatment	20	12.19	12	8.05	16	10.06
Mean Total Daily OFF time at Baseline of less than 2.5 hours	1	0.60	.	.	2	1.25
Premature Termination from the Study	22	13.41	17	11.4	19	11.94
Study Drug Compliance of Less than 70%	2	1.21	1	0.67	1	0.62
Use of Anti-Emetics and Neuroleptics With Central Dopamine Antagonist Activity Within 6 Months Prior to Randomization or During the Study	.	.	2	1.34	2	1.25
All (At least one Protocol Violation)	39	23.8	30	20.1	44	27.7

Cross-reference: Individual data listing of Protocol Deviations in Appendix 16.2.3.1

Cross-reference: Individual data listing of Rasagiline Compliance in Appendix 16.2.3.2

Demographics and other Baseline Characteristics

Demographics

In this North American trial, 472 subjects were enrolled at 57 study sites in the United States (49 sites) and Canada (8 sites). The distribution of subjects by country is displayed in Table 78. The distribution of subjects by country and by study site is presented in Table 78. The distribution of subjects in each treatment group was similar in both countries.

CLINICAL REVIEW

Table 78 Distribution of Subjects by Country

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Country								
Canada	20	12.2	15	10.1	19	11.9	54	11.4
USA	144	87.8	134	89.9	140	88.1	418	88.6
All	164	100.0	149	100.0	159	100.0	472	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4.1

The great majority of subjects (91%) from all treatment groups were white. In all treatment groups there were more male than female subjects (Table 79). There were no statistically significant differences in sex between the treatment groups.

Table 79 Distribution of Subjects by Sex

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Gender								
Female	62	37.8	50	33.6	55	34.6	167	35.4
Male	102	62.2	99	66.4	104	65.4	305	64.6
All	164	100.0	149	100.0	159	100.0	472	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4.1

Descriptive statistics for age, and the distribution of subjects by age categories are shown in Table 80 respectively. For the 3 treatment groups the mean age was between 63 and 65 years. From the 2 rasagiline treatment groups approximately 42% of subjects were equal to or older than 65 years, while for the placebo treatment group 52% of subjects were equal to or older than 65 years. There were no statistically significant differences between the treatment groups.

Table 80 Distribution of Subjects by Age Category

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Age Category								
54 or Less	36	22.0	29	19.5	28	17.6	93	19.7
55<=Age<65	59	36.0	58	38.9	49	30.8	166	35.2
65<=Age<75	54	32.9	47	31.5	60	37.7	161	34.1
75<=Age	15	9.1	15	10.1	22	13.8	52	11.0
All	164	100.0	149	100.0	159	100.0	472	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4.1

There were no statistically significant differences between treatment groups for height and weight.

Parkinson's Disease Characteristics

On entry into the study, the treatment groups had a mean PD duration ranging from 8.8 to 9.7 years. All subjects were on chronic levodopa treatment and each treatment group had a levodopa treatment duration of approximately one year less than their mean PD (range 7.9 to 8.5 years) (Table 81). All subjects were experiencing motor fluctuations – the mean fluctuation duration ranged from 3.7 years to 4.4 years for the 3 treatment groups. Overall, 337 (71%) patients entered the study with dyskinesia. For the 115 subjects in the 0.5 mg/day rasagiline treatment group a mean dyskinesia duration of 4.6 years was obtained. For the 105 subjects in the 1 mg/day rasagiline treatment group a mean dyskinesia duration of 3.7 years was obtained, and

CLINICAL REVIEW

for the 117 patients in the placebo treatment group a mean dyskinesia duration of 4.4 years was obtained. There were no statistically significant differences between the treatment groups for any of these baseline disease characteristics.

Table 81 Descriptive Statistics of Parkinson's Disease History

TVP-1012/133 (PRESTO)		0.5 mg	1 mg	Placebo	All
PD Duration (years)	N	164	149	159	472
	Mean	9.32	8.83	9.68	9.29
	Median	8.1	7.9	9.3	8.2
	Std	5.6	5.4	4.9	5.3
	Min	0.76	0.79	0.48	0.48
	Max	29.9	33.3	25.3	33.3
Levodopa Treatment Duration (years)	N	164	149	159	472
	Mean	8.28	7.87	8.53	8.23
	Median	7.0	6.9	8.1	7.4
	Std	5.5	5.4	4.7	5.2
	Min	0.52	0.59	0.48	0.48
	Max	27.9	32.0	21.3	32.0
Fluctuations Duration (years)	N	164	149	159	472
	Mean	4.43	3.71	4.24	4.14
	Median	3.1	2.8	3.4	3.1
	Std	4.4	3.1	3.3	3.7
	Min	0.13	0.08	0.16	0.08
	Max	23.2	19.2	16.0	23.2
Dyskinesia Duration (years)	N	115	105	117	337
	Mean	4.57	3.67	4.44	4.25
	Median	3.5	2.7	3.4	3.3
	Std	4.1	3.8	3.4	3.8
	Min	0.01	0.08	0.14	0.01
	Max	21.9	26.0	13.9	26.0

Cross-reference: Individual data listing of Parkinson's Disease History in Appendix 16.2.4.2

At baseline, the 0.5 mg/day rasagiline, 1 mg/day rasagiline and placebo treatment groups were receiving a mean total daily levodopa dose of 750 mg, 815 mg, and 821 mg respectively. There were no statistically significant differences between the treatment groups.

Treatment groups were not statistically different at baseline with regard to "24-hour" diary parameters (Table 82).

CLINICAL REVIEW

Table 82 Descriptive Statistics of Baseline “24-Hour” Diary Parameters

TVP-1012/133 (PRESTO)		0.5 mg	1 mg	Placebo	All
Mean Total Daily Waking Time* (hours) (Baseline)	N	164	149	159	472
	Mean	16.58	16.66	16.69	16.64
	Std	1.58	1.39	1.52	1.50
	Median	16.50	16.67	16.50	16.50
	Min	11.00	11.33	13.33	11.00
	Max	22.50	19.83	21.83	22.50
Mean Total Daily "OFF" Time (hours) (Baseline)	N	164	149	159	472
	Mean	6.05	6.27	5.97	6.09
	Std	2.04	2.55	2.21	2.27
	Median	5.83	5.67	5.83	5.83
	Min	0.00	2.67	1.17	0.00
	Max	13.67	15.50	12.83	15.50
Mean Total Daily "ON" Time† (hours) (Baseline)	N	164	149	159	472
	Mean	10.53	10.38	10.72	10.55
	Std	2.26	2.63	2.24	2.38
	Median	10.58	10.67	10.67	10.67
	Min	5.00	0.83	4.17	0.83
	Max	19.67	15.67	16.33	19.67
Mean Total Daily "ON1" Time (hours) (Baseline)	N	164	149	159	472
	Mean	9.47	9.42	9.76	9.55
	Std	2.59	3.01	2.63	2.74
	Median	9.58	9.83	9.83	9.83
	Min	0.00	0.00	1.50	0.00
	Max	15.67	15.67	16.33	16.33
Mean Total Daily "ON2" Time (hours) (Baseline)	N	164	149	159	472
	Mean	1.07	0.97	0.96	1.00
	Std	2.19	2.03	1.72	1.99
	Median	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00
	Max	11.67	11.50	8.17	11.67

* "ON" = "ON1" + "ON2"

Cross-reference: Individual data listing of Derived “24-Hour” Diary Parameters (Baseline, Treatment, Change) in Appendix 16.2.5.1

Cross-reference: Individual data listing of Raw “24-Hour” Diary Data in Appendix 16.2.5.3

Cross-reference: Individual data listing of Per-Day “24-Hour” Diary Data in Appendix 16.2.5.4

UPDRS sub-scales and “total” UPDRS scores (sum of mental, AD-“on” and motor-“on” subscales) were similar for all treatment groups. Mean scores for all groups were 28-29 for “total” UPDRS, ~ 2 for UPDRS mental, ~ 6 for ADL “ON,” ~ 16 for ADL “OFF,” ~ 21 for UPDRS “ON,” and ~ 1 for UPDRS dyskinesia. Baseline PD-QUALIF scores, Item 33 PD-QUALIF scores, Severity of Illness scores, examiner and subject Schwab and England scores in the “ON” and “OFF” states, in Beck Depression Inventory scores, and MMSE scores were similar across all treatment groups. There were no statistically significant differences between the treatment groups at baseline for these various scores.

Hoehn and Yahr staging at screening resulted in scores of approximately 2.0 and 2.6 units for “ON” and “OFF” states respectively and were similar for all treatment groups

Past and Concomitant Medical Conditions Unrelated to Parkinson's Disease

As expected from this elderly patient population, subjects entered the study with other medical conditions besides Parkinson’s Disease. There were no noteworthy differences among the treatment groups. The concurrent medical conditions that were seen in the greatest number of subjects overall were related to the following body systems: musculoskeletal (68%),

CLINICAL REVIEW

cardiovascular / gastrointestinal / genitor-urinary (each approximately 53%) and psychiatric / neurological / ophthalmologic (each approximately 41% to 43%).

Prior and Concomitant Medications for Parkinson's Disease

PD medications taken during the year preceding the study and/or during the study, and non-PD medications taken at least once during the 3 months preceding the study and/or during the study were recorded.

A review and comparison of individual medications taken before and during the study indicates that medications that were discontinued prior to the trial generally corresponded to those prohibited by the protocol: investigational drugs, dopamine antagonists, selegiline, tolcapone, amphetamine and related stimulants, as well as several herbal and homeopathic preparations. There were no apparent differences among treatment groups in the profile of prior or concomitant medications taken.

In addition to anti-PD medications, classes of medications taken by the largest percent of subjects during the study were analgesics and anti-inflammatory agents (67% of subjects overall), nutritional agents and vitamins (49% of subjects overall), cardiovascular and gastrointestinal agents (each with an overall incidence of 39%).

Antidepressants were taken by 25% of subjects overall. Specific agents reflect medications permitted by the protocol in low doses: the tri- and tetracyclic antidepressants, amitriptyline and trazodone, as well as the serotonin reuptake inhibitors citalopram, paroxetine and sertraline. These antidepressants were taken by subjects in all three treatment groups.

Concomitant PD medications are displayed by group in Table 83. Approximately 86% of subjects from all treatment groups took other PD medications during the study besides the study drug and besides immediate release levodopa. The group of PD medications taken with the highest incidence (approximately 70% in each treatment group) was the dopamine agonists of which pramipexole, followed by pergolide and ropinirole were the most commonly used. The COMT inhibitor, entacapone, was being used by approximately one-third of all subjects, while amantadine was used with an incidence of approximately 20% in each treatment group. Fewer than 10% of subjects were taking concomitant antimuscarinics as PD therapy.

Table 83 Concomitant PD Medications by Drug or Drug Group

TVP-1012/133 (PRESTO)	0.5 mg (N=164)		1 mg (N=149)		Placebo (N=159)	
	N	%	N	%	N	%
- ALL	142	86.6	129	86.6	133	83.6
AMANTADINE HYDROCHLORIDE	34	20.7	26	17.4	38	23.9
ANTIMUSCARINIC AGENTS	14	8.5	11	7.4	15	9.4
COMT INHIBITOR	55	33.5	49	32.9	61	38.4
DOPAMINE AGONISTS	113	68.9	106	71.1	111	69.8

Only anticholinergic medications used to treat PD are included

Cross-reference: Individual data listing of Concomitant Medications in Appendix 16.2.4.5

CLINICAL REVIEW

Primary Efficacy Endpoint - Change from Baseline during Treatment in the Mean Total Daily “OFF” Time

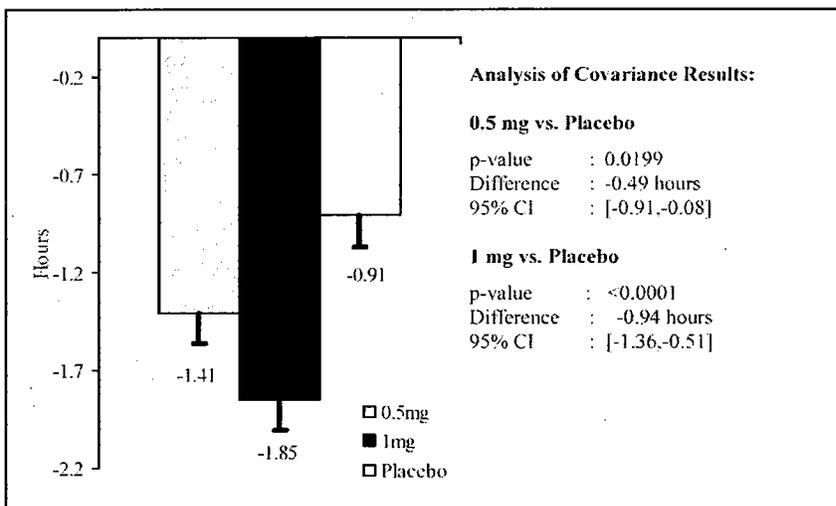
The primary endpoint for this trial was the change from baseline during treatment in the mean total daily “OFF” time.

ITT Cohort

The principal efficacy analysis for this study was the baseline adjusted analysis of covariance for the ITT cohort presented in Figure 34. The mean baseline total daily “OFF” time was 6.0 hours for the 0.5 mg/day rasagiline treatment group, 6.3 hours for the 1 mg/day rasagiline treatment group, and 6.0 hours for the placebo-treated arm.

Analysis of Covariance (Figure 34) results in an adjusted mean decrease from baseline in the total daily “OFF” time of 1.41 hours for the 0.5 mg/day rasagiline treatment group, 1.85 hours for the 1 mg/day rasagiline treatment group and 0.91 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction of 0.49 hours ($p=0.0199$) for 0.5 mg/day rasagiline over placebo and of 0.94 hours ($p<0.0001$) for 1 mg/day rasagiline over placebo.

Figure 34 Principal Analysis: Adjusted Mean Change from Baseline During Treatment in Total Daily “OFF” Time for ITT Cohort



Cross-reference: Statistical Output for “24-Hour” Diary Analyses in Appendix 16.1.9.4.2.

Completer (CO) and Per-Protocol (PP) Cohorts

The analyses of the primary endpoint conducted for the CO and PP cohorts confirm the results and conclusions of the principal analysis of the ITT cohort in both magnitude of the clinical effect and level of statistical significance.

For the CO cohort, the mean baseline total daily “OFF” time was 6.1 hours for the 0.5 mg/day rasagiline treatment group, 6.2 hours for the 1 mg/day rasagiline treatment group and 6.0 hours

CLINICAL REVIEW

for the placebo-treated arm. Analysis of Covariance results in an adjusted mean reduction from baseline in the total daily “OFF” time of 1.49 hours for the 0.5 mg/day rasagiline treatment group, 1.89 hours for the 1 mg/day rasagiline treatment group and 0.95 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction 0.54 hours ($p=0.0156$, 95% CI: -0.97, -0.10) for 0.5 mg/day rasagiline over placebo and 0.94 hours ($p<0.0001$, 95% CI: -1.38, -0.49) for 1 mg/day rasagiline over placebo.

For the Per-Protocol Cohort, the mean total daily “OFF” time was 6.1 hours for the 0.5 mg/day rasagiline treatment group, 6.2 hours for the 1 mg/day rasagiline treatment group and 6.0 hours for the placebo-treated arm. The Analysis of Covariance results in an adjusted mean reduction from baseline in the total daily “OFF” time of 1.52 hours for the 0.5 mg/day rasagiline treatment group, 1.99 hours for the 1 mg/day rasagiline treatment group and 0.91 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction 0.62 hours ($p=0.0087$, 95% CI: -1.08, -0.16) for 0.5 mg/day rasagiline over placebo and 1.08 hours ($p<0.0001$, 95% CI: -1.55, -0.61) for 1 mg/day rasagiline over placebo.

Analysis of “ON” and “ON1”

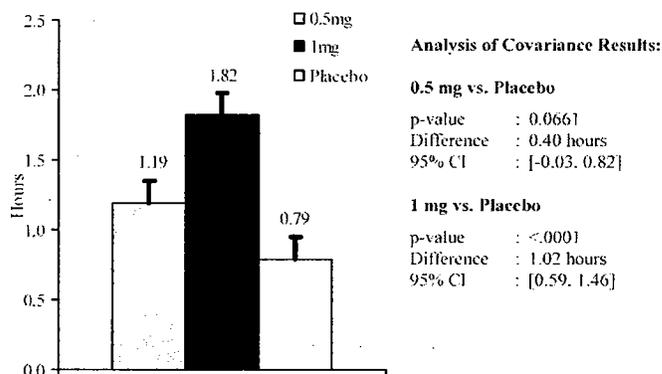
For each diary day, the total daily “OFF”, “ON1” and “ON2” time was calculated. The change between the mean of the diaries during the treatment period to the mean of the diaries during the baseline period is defined as the change from baseline to treatment period in the mean of total daily “OFF” time, “ON1” time (without troublesome dyskinesia), “ON2” time (with troublesome dyskinesia), and “ON” time (“ON”=“ON1”+“ON2”).

Post-hoc analysis (included in the SAP but not in the protocol nor amendments) of total daily “ON” (calculated from the sum of “ON1” and “ON2”) and “ON1” and “ON2” times in order to better characterize the reduction of the “OFF” time reveals that the decrease in the total daily “OFF” can be accounted for by the increase in the total daily “ON” time. The mean total daily “ON” time at baseline was 10.5 hours for the 0.5 mg/day rasagiline treatment group, 10.4 hours for the 1 mg/day rasagiline treatment group and 10.7 hours for the placebo-treated arm.

Analysis of Covariance results in an adjusted mean increase from baseline in the total daily “ON” time of 1.19 hours for the 0.5 mg/day rasagiline treatment group, 1.82 hours for the 1 mg/day rasagiline treatment group and 0.79 hours for the placebo treatment arm with an overall statistically significant increase of 1.02 hours for the 1 mg/day rasagiline treatment group over placebo ($p < 0.0001$) (Figure 35). The difference of 0.4 hours between the 0.5 mg/day rasagiline treatment group and the placebo treatment group in the change from baseline in total daily “ON” time does not reach statistical significance ($p = 0.0661$, 95% CI: -0.03, 0.82).

CLINICAL REVIEW

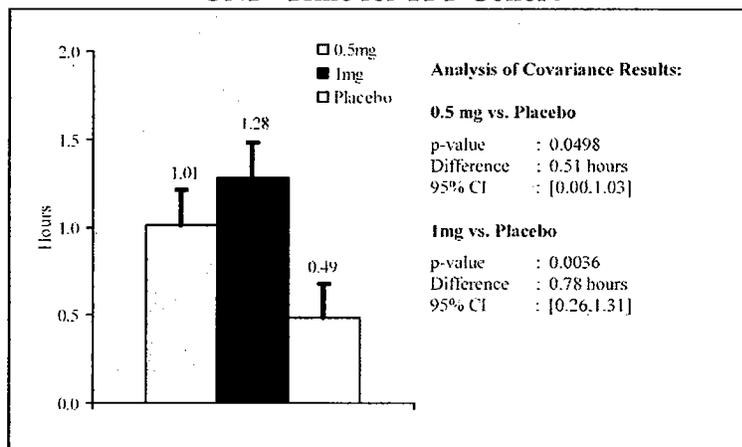
Figure 35 Adjusted Mean Change from Baseline During Treatment in Total Daily “ON” Time for ITT Cohort



Cross-reference: Statistical Output for “24-Hour” Diary Analyses in Appendix 16.1.9.4.2.

Further exploratory significance testing shows that the increase in the total daily “ON” time is largely due to the increase in the total daily “ON1” time. The mean baseline total daily “ON1” time was 9.5 hours for the 0.5 mg/day and 1 mg/day rasagiline treatment groups while for the placebo treatment group it was 9.7 hours. Analysis of Covariance (Figure 36) results in an adjusted mean increase from baseline in the total daily “ON1” time of 1.01 hours for the 0.5 mg/day rasagiline treatment group, 1.28 hours for the 1 mg/day rasagiline treatment group and 0.49 hours for the placebo treatment arm with an overall statistically significant increase of 0.51 hours ($p = 0.0498$) for the 0.5 mg/day rasagiline treatment group over placebo and of 0.78 hours ($p = 0.0036$, 95% CI: 0.26, 1.31) for the 1 mg/day rasagiline treatment group over placebo. The difference between the rasagiline and placebo treatment groups in the change from baseline in the mean total daily “ON2” time is detailed in the safety section.

Figure 36 Adjusted Mean Change from Baseline During Treatment in Total Daily “ON1” Time for ITT Cohort



Cross-reference: Statistical Output for “24-Hour” Diary Analyses in Appendix 16.1.9.4.2.

CLINICAL REVIEW

Secondary Efficacy Endpoints

Analysis of the primary endpoint of the study has demonstrated a highly statistically significant drug effect across all subject cohorts with comparable magnitude of clinical relevance and statistical significance. Therefore, the analyses of secondary and additional efficacy endpoints, as predefined in the SAP, are limited to the ITT cohort.

As originally planned, the Hierarchical Approach was implemented for controlling for the type-I error due to multiple testing. This approach dictates that secondary endpoints can be tested at the alpha level of 5%, sequentially in a pre-defined order, if and only if statistical significance for the primary endpoint is demonstrated.

- The hierarchical order for the 4 secondary endpoints of this study is:
- Global Improvement by the Examiner.
- Change from Baseline to Last Observed Value in UPDRS ADL during “OFF” state.
- Change from Baseline to Last Observed Value in UPDRS Motor during “ON” State.
- Change from Baseline to termination in Quality of Life (QOL) Scale (PD-QUALIF)

This analysis plan was not specified in the protocol nor in protocol amendments but was included in the sponsor’s Statistical Analysis Plan (SAP). The sponsor informed me that the SAP was submitted to FDA/DNDP approximately 1 month before the blind was broken in this study.

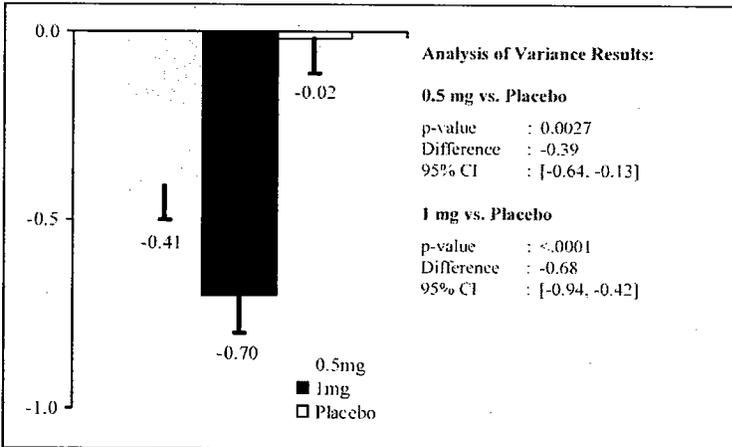
The sponsor did not present statistical analyses for the results for the changes for the secondary efficacy endpoints per se but only presented the statistical results for the ANCOVA model and adjusted means according to the model. Dr. Yan (Statistician) conducted analyses showing unadjusted means. Mean results were usually very similar.

Global Improvement by the Examiner

As assessed by the examiner, as of the end of the study, the mean values for Global Improvement scores decreased (i.e., improved) by 0.40 units for the 0.5 mg/day rasagiline treatment group, by 0.66 units for the 1 mg/day rasagiline treatment group, and by 0.02 units for the placebo treatment group. Analysis of Variance (Figure 37) results in an adjusted mean decrease for Global Improvement scores of 0.41 units for the 0.5 mg/day rasagiline treatment group, 0.70 units for the 1 mg/day treatment group, and 0.02 units for the placebo treatment group with an overall statistically significant reduction of 0.39 units ($p=0.0027$, 95% CI: -0.64, -0.13) for 0.5 mg/day rasagiline and of 0.68 units ($p<0.0001$, 95% CI: -0.94, -0.42) for 1 mg/day rasagiline relative to placebo.

CLINICAL REVIEW

Figure 37 Adjusted Mean Global Improvement by Examiner

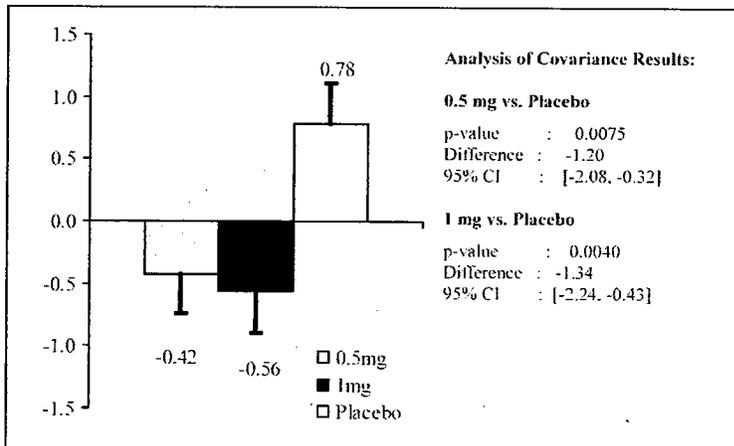


Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

Change from Baseline to Termination in UPDRS ADL during "OFF" State

The mean baseline UPDRS ADL "OFF" was 15.7 units for the 0.5 mg/day rasagiline treatment group, 15.6 units for the 1 mg/day rasagiline treatment group and 15.5 points for the placebo treatment group. Analysis of Covariance (Figure 38) results in a decrease of 0.42 points for the 0.5 mg/day rasagiline treatment group and of 0.56 units for the 1 mg/day treatment group, whereas for the placebo treatment group there was an increase of 0.78 units. There was an overall statistically significant reduction of 1.20 units ($p=0.0075$, 95% CI: -2.08, -0.32) for 0.5 mg/day rasagiline over placebo and of 1.34 units ($p<0.0040$, 95% CI: -2.24, -0.43) for 1 mg/day rasagiline over placebo.

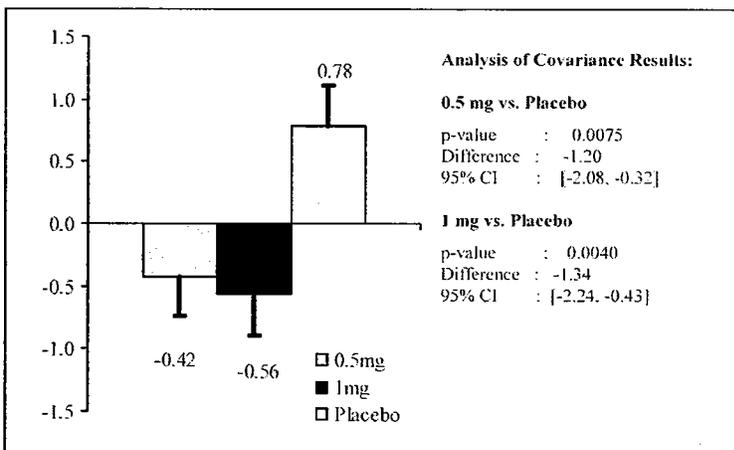
Figure 38 Adjusted Mean Change from Baseline in UPDRS ADL "OFF"



Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

CLINICAL REVIEW

Figure 39 Adjusted Mean Change from Baseline in UPDRS ADL “OFF”

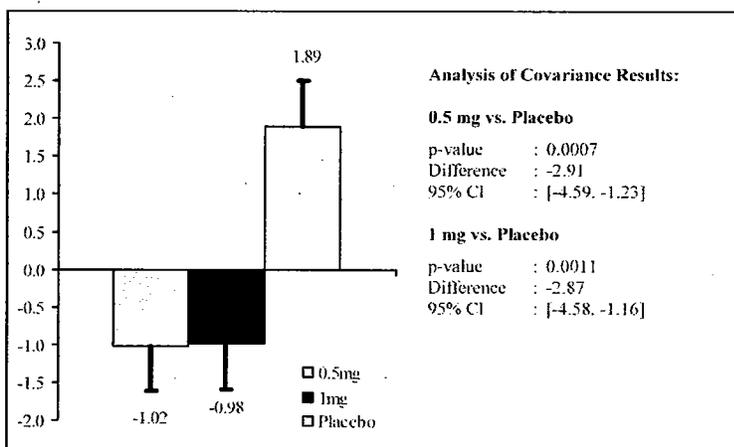


Cross-reference: Statistical Output for Efficacy Analyses besides “24-Hour” Diary Analyses in Appendix 16.1.9.4.3.

Change from Baseline to Last Observed Value in UPDRS Motor during “ON” State

The mean UPDRS Motor “ON” was 21.4 units for the 0.5 mg/day rasagiline treatment group, 21.0 units for the 1 mg/day rasagiline treatment group and 20.8 units for the placebo treatment group. Analysis of Covariance (Figure 40) results in an adjusted mean decrease of 1.02 units for the 0.5 mg/day rasagiline treatment group and of 0.98 units for the 1 mg/day rasagiline treatment group, whereas for the placebo treatment group there was an adjusted mean increase of 1.89 units. There was an overall statistically significant reduction of 2.91 units ($p=0.0007$, 95% CI: -4.59, -1.23) for 0.5 mg/day rasagiline over placebo and of 2.87 units ($p=0.0011$, 95% CI: -4.58, -1.16) for 1 mg/day rasagiline over placebo.

Figure 40 Adjusted mean Change from Baseline in UPDRS Motor “ON”



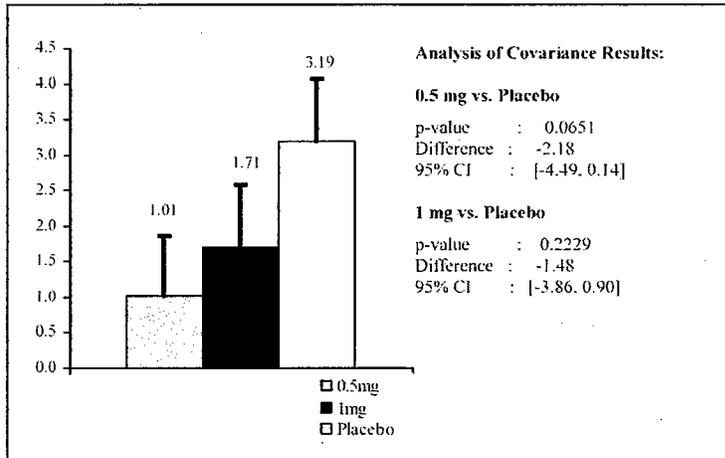
Cross-reference: Statistical Output for Efficacy Analyses besides “24-Hour” Diary Analyses in Appendix 16.1.9.4.3.

Change from Baseline to Termination in PD-QUALIF

CLINICAL REVIEW

Summary statistics given in as well as the Analysis of Covariance shown in Figure 41 provide no evidence to suggest that rasagiline treatment significantly affected PD-QUALIF scores.

Figure 41 Adjusted Mean Change from Baseline in Parkinson's Disease-QUALIF Scores



Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

Additional Efficacy Endpoints

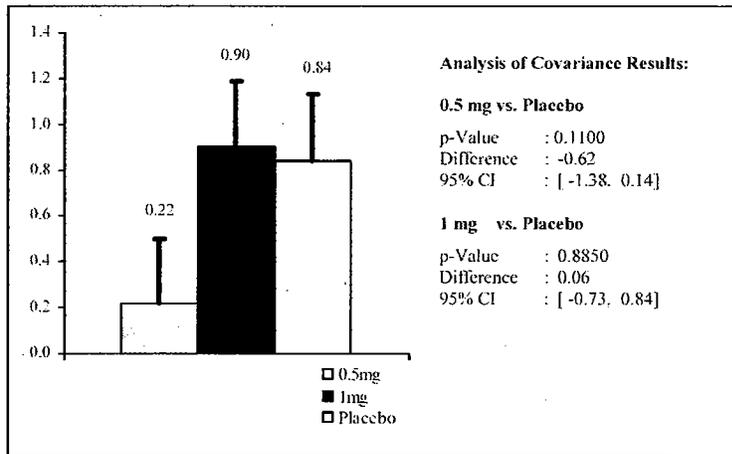
Several additional efficacy endpoints, some of which had been mentioned in the protocol as exploratory efficacy endpoints, were pre-defined in the SAP and were presented in this report in order to better explore the consistency of the rasagiline effect. These endpoints were tested at a nominal alpha level of 5%.

Most of these efficacy endpoints were not considered significant endpoints in the protocol. Thus, I will not present these efficacy data in any detail with the exception of change from baseline for ADL "on" that had been identified in the protocol as a secondary efficacy endpoint. However, I will show the treatment effect of 1 mg/day rasagiline in a summary table of many efficacy endpoints predefined in the SAP for this clinical trial (Table 84).

Change from Baseline to Termination in UPDRS ADL during "ON" State

The baseline mean UPDRS ADL "ON" score was 5.6 units for the 0.5 mg/day rasagiline treatment group, 5.7 units for the 1 mg/day rasagiline treatment group and 6.1 units for the placebo treatment group. Analysis of Covariance (Figure 42) results in adjusted mean increases of 0.22 units for the 0.5 mg/day rasagiline treatment group, 0.90 units for the 1 mg/day rasagiline treatment group and of 0.84 units for the placebo treatment group. There are no statistically significant differences for either of the rasagiline treatment groups over placebo.

Figure 42 Adjusted Mean Change from Baseline to Termination in UPDRS ADL “ON”



Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

Repeated Measures Analysis of the Change from Baseline to Each Treatment Visit in the Mean Total Daily .OFF. Time

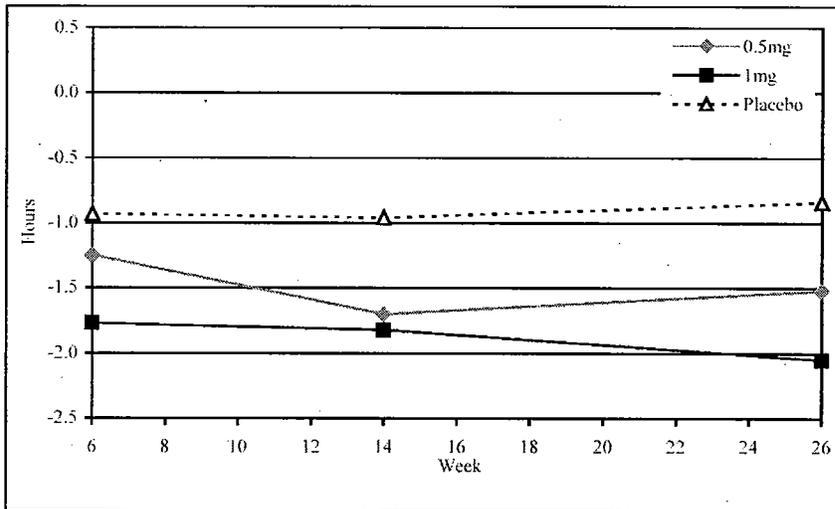
Figure 43 that displays descriptive statistics of mean total daily "OFF" time and the change from baseline by actual week in trial reveal that the beneficial effect of rasagiline over placebo is already pronounced by visit 2/week 6, the first post-randomization diary visit. Repeated measures analysis (Figure 43) of baseline adjusted Covariance demonstrates that the beneficial effect of rasagiline relative to placebo is evident across all study visits. Repeated measures contrasts for both rasagiline treatment groups versus placebo are statistically significant, demonstrating that across visits the total daily "OFF" time is reduced with rasagiline treatment :

- rasagiline 0.5 mg/day vs. placebo contrast: 0.49 hours (p=0.0172, 95% CI: -0.90, -0.09).
- rasagiline 1 mg/day vs. placebo contrast: 0.89 hours (p<0.0001, 95% CI: -1.30, -0.47).

A refined assessment of the consistency of the effect size across visits suggests no statistically significant treatment-by-week interaction (p=0.4848). In conclusion, the repeated measures analysis of covariance confirms that the rasagiline effect of reducing the mean total daily "OFF" time that was seen for both study doses was consistent and robust across visits and in line with the baseline to termination analysis.

CLINICAL REVIEW

Figure 43 Change from Baseline to Each Visit in the Mean Total Daily “OFF” Time



Cross-reference: Statistical Output for "24-Hour" Diary Analyses in Appendix 16.1.9.4.2.

Repeated Measures Analysis of Covariance

Time effect was found to be non-significant between groups (p=0.4848)

Parameter		Estimate	P-Value	95% CI	
				Lower	Upper
Common Slope		-0.003	0.5676	-0.015	0.008
0.5 mg vs Placebo	-Intercept	-0.491	0.0172	-0.895	-0.088
1 mg vs Placebo	-Intercept	-0.888	<.0001	-1.302	-0.473
0.5 mg vs 1 mg	-Intercept	0.396	0.0579	-0.013	0.806

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CLINICAL REVIEW

Table 84 Summary of Efficacy Endpoints

End-Point	Treatment Effect of Rasagiline 1 mg/day compared to Placebo*	p-value	95% CI
Primary Endpoint			
Adjusted Mean Change from Baseline during Treatment in Total Daily "OFF" Time (ITT Cohort)	-0.94 hours	< 0.0001	-1.36 to -0.51
Adjusted Mean Change from Baseline during Treatment in Total Daily "OFF" Time (Completers Cohort)	-0.94 hours	< 0.0001	-1.38 to -0.49
Adjusted Mean Change from Baseline during Treatment in Total Daily "OFF" Time (Per Protocol Cohort)	-1.08 hours	< 0.0001	-1.55 to -0.61
Secondary Endpoints			
(#1) Global Improvement by the Examiner	-0.68 units	< 0.0001	-0.94 to -0.42
(#2) Change from Baseline to Termination in UPDRS ADL During "OFF" State	-1.34 units	0.0040	-2.24 to -0.43
(#3) Change From Baseline to Termination in UPDRS Motor During "ON" State	-2.87 units	0.0011	-4.58 to -1.16
(#4) Change from Baseline to Termination in Quality of Life (QOL) Score (PD-QUALIF)	-1.48	0.2229	-3.86 to 0.90
Additional Endpoints			
Categorical Change from Baseline in the Mean Total Daily "OFF" Time (Responder Analysis)	Odds ratio of 2.5	0.0005	1.49 to 4.23
Change from Baseline to Termination in the Mean Total Daily "OFF" Time	-0.89 hours	0.0080	-1.55 to -0.23
Repeated Measures Analysis of the Change from Baseline to Each Treatment Visit in the Mean Total Daily "OFF" Time	-0.89 hours	< 0.0001	-1.30 to -0.47
Change from Baseline to Termination in Severity of Illness	-0.07 units	0.3121	-0.22 to 0.07
Global Improvement by Subject	-0.75 units	< 0.0001	-1.04 to -0.46
Change from Baseline to Termination in QOL Item 33 (PD Symptoms compared to 3 months ago)	-0.36 units	0.0003	-0.56 to -0.17
Change from Baseline to Termination in UPDRS ADL During "ON" State	0.06 units	0.8850	-0.73 to 0.84
Change from Baseline to Termination in Examiner Schwab and England ADL "OFF" Score	3.0%	0.0183	0.51 to 5.48
Change from Baseline to Termination in Subject Schwab and England ADL "OFF" Score	3.2%	0.0267	0.37 to 6.04
Change from Baseline to Termination in Examiner Schwab and England ADL "ON" Score	0.7%	0.4491	-1.03 to 2.32
Change from Baseline to Termination in Subject Schwab and England ADL "ON" Score	1.4%	0.1454	-0.48 to 3.23
Change from Baseline in Total Daily Levodopa Dose	-18.6 mg	0.2397	-49.7 to 12.5

* Treatment effect = [Adjusted mean change from baseline for the rasagiline 1 mg/day treatment group] - [Adjusted mean change from baseline for the placebo treatment group]

CLINICAL REVIEW

Subgroup Analyses

Post hoc subgroup analyses have been performed after pooling data from the rasagiline 1 mg treatment groups and from the placebo treatment groups from LARGO (TVP-1012/122) and PRESTO (TVP-1012/133). Analyses have been performed on the primary efficacy endpoint, the change from baseline to treatment in the total daily “OFF” time and on the 3 secondary endpoints common to both studies. I am presenting only the sponsor’s results for the primary efficacy endpoint.

For the primary efficacy endpoint the interactions between treatment and sex, age category (< 65 years, ≥ 65 years), baseline total daily LD dose (< 500 mg, 500 - < 1000 mg, ≥ 1000 mg), dopamine agonist use, baseline Hoehn and Yahr stage while “ON” (≤ 2 units, > 2 units), LD treatment duration (as a continuous variable) and Parkinson’s disease duration (as a continuous variable) have been analyzed. The original predefined ANCOVA model for analysis of the primary efficacy endpoint included the baseline mean total daily “OFF” time as a covariate, in addition to the treatment, study and center within study as fixed effects as well as treatment-by-study interaction term. For each subgroup analysis the model also included the relevant variable as well as its interaction term with treatment to examine homogeneity of treatment effect by each variable level.

As seen in Table 85 by the p-values of interaction between treatment and each variable, the effect of treatment was not related to age, sex, baseline total daily LD dose, duration of Parkinson’s disease or to levodopa treatment, and concomitant dopamine agonist use. The statistically significant different treatment effect of the Hoehn and Yahr stage when “ON” (p-value for interaction term = 0.0454), with a larger adjusted mean treatment effect of rasagiline in subjects with a Hoehn and Yahr stage = 2 versus subjects with a Hoehn and Yahr stage >2 (n=255 and 109, respectively), is possibly a chance finding. In any case, the effects in the two Hoehn and Yahr categories are in favor of rasagiline group and only the effect sizes are different.

Table 85 Subgroup/Subpopulation Analyses of Primary Efficacy Endpoint for Pooled Data from Adjunctive Pivotal Trials (PRESTO and LARGO)

Rasagiline SCE: Placebo-Controlled Studies (Phase III) Levodopa-Treated Fluctuating Patients		Treatment				P-value	
		Rasagiline 1 mg		Placebo		Treatment Effect between Rasagiline 1 mg and Placebo	Interaction between Treatment and Variable
		Adjusted Mean	SE	Adjusted Mean	SE		
Sex	Male	-1.50	0.14	-0.67	0.15	<0.0001	0.8544
	Female	-1.40	0.20	-0.51	0.19		
Age Category	65 years or more	-1.79	0.17	-0.62	0.16	<0.0001	0.0804
	Less than 65 years	-1.20	0.16	-0.60	0.17		
Hoehn & Yahr Stage	H&Y > 2	-1.20	0.22	-0.80	0.19	<0.0001	0.0454
	H&Y ≤ 2	-1.58	0.14	-0.50	0.15		
Dopamine Agonists Treatment	With DA Treatment	-1.58	0.14	-0.66	0.15	<0.0001	0.5506
	W/O DA Treatment	-1.24	0.21	-0.52	0.20		
Baseline Total Daily LD Dose	<500 mg	-1.40	0.24	-0.50	0.25	<0.0001	0.2118
	500 to <1000 mg	-1.60	0.17	-0.53	0.16		
	≥1000 mg	-1.25	0.24	-0.88	0.25		
PD Duration	years	-1.47	0.12	-0.59	0.12	0.0001	0.1724
LD Treatment Duration	years	-1.47	0.12	-0.60	0.12	<0.0001	0.1374

CLINICAL REVIEW

11.2.3. Sponsor's Discussion of Results of Study TVP-1012/133 PRESTO

The sponsor did not present a discussion of study results.

11.2.4. Sponsor's Conclusions

This study has demonstrated that a daily dose of rasagiline is effective in decreasing "OFF" time in levodopa-treated PD patients experiencing motor fluctuations. The difference between rasagiline and placebo treatments (in favor of rasagiline) in the change from baseline in the total daily "OFF" time is 0.94 hours for the 1 mg/day rasagiline treatment group, and 0.49 hours for the 0.5 mg/day rasagiline treatment group.

The beneficial effect of rasagiline is present across all study cohorts representing the internal consistency of the data and the adequacy of the conduct of the trial. Furthermore, the highly statistical significant outcome of the principal analysis of this study has been demonstrated to be conclusive and robust by a variety of alternative and complementary analysis models. The numerically and clinically superior effect detected in the 1 mg/day rasagiline-treatment arm compared to the 0.5 mg/day rasagiline-treatment arm suggests a dose relationship.

The beneficial effect of 1 mg/day rasagiline over placebo is already evident at visit 2/week 6, the first post-randomization diary visit, and is maintained across all study visits including the termination visit. The beneficial effect is obtained even though subjects were on optimized levodopa treatment and, most subjects were taking adjunctive antiparkinson medications including dopamine agonists, which themselves have the ability to improve fluctuations. The clinical relevance of the primary endpoint data is confirmed by the "responder" analysis, based on the percentages of subjects with an improvement in total daily "OFF" time of at least 60 minutes. The reduction in the total daily "OFF" time corresponds closely to the increase in the total daily "ON", and the increase in the total daily "ON" time is due primarily to an increase in "ON1" time i.e., "ON without dyskinesia or without troublesome dyskinesia".

Analyses of the secondary endpoints that were adjusted for multiplicity have demonstrated an overall statistically significant treatment effect that was attributable to rasagiline treatment for all 3 clinical secondary endpoints: Global Improvement rated by the Examiner, UPDRS ADL in "OFF" state, and UPDRS Motor in the "ON" state. The improvement in UPDRS Motor score in the "ON" state is notable since subjects entered the study on optimal doses of levodopa. The further improvement in the "ON" state scores suggests that rasagiline may not only extend the duration of levodopa benefit but may also enhance its maximal antiparkinsonian effect. The improvement in the UPDRS ADL in "OFF" state suggests that in addition to the beneficial effect of rasagiline in reducing OFF time, rasagiline also lessens the severity of "OFF". This is further supported by the results for Examiner- and Subject-rated Schwab and England ADL scores during the "OFF" state that demonstrate the beneficial effect of rasagiline treatment.

Although there is no evidence confirming a treatment effect for the 4th secondary endpoint measuring subjects' quality of life with the PD-QUALIF scale, rasagiline has shown a benefit over placebo for item 33 of the PD-QUALIF scale.

CLINICAL REVIEW

A statistically significant treatment effect over placebo of rasagiline 1 mg/day is seen in the in Global Improvement score as rated by the subject. The similarity between results obtained for the Examiner's and Subject's Global Improvement scores supports the selection of Global Improvement (Examiner's score) as the first in the hierarchy of the secondary endpoints.

Post-hoc analyses have shown statistically significant differences between rasagiline and placebo treatments in the change from baseline in the Total UPDRS score and UPDRS subscales rating tremor, rigidity and bradykinesia.

Rasagiline treatment has also shown a small decrease in the mean total daily levodopa dose that did not reach statistical significance. The design of this study did not permit levodopa dose reduction except in the case of intolerability and only during the first 6 weeks of the study. Perhaps if more leeway had been allowed, a larger reduction in total daily levodopa dose might have been observed.

There were no statistically significant differences between the rasagiline and placebo treatment groups regarding changes from baseline in the UPDRS ADL "ON", PD-QUALIF (the QoL scale), Examiner- and Subject-rated Schwab and England ADL score for the subject's "ON" state.

11.2.5. Reviewer's Comments

- The sponsor did not present nor discuss results of the unadjusted mean values for the primary efficacy endpoint nor for the secondary efficacy endpoints.
-
- Table 86 shows results for the unadjusted mean change of the primary efficacy endpoint for all treatment groups based upon the analyses of the statistical reviewer, Dr. Sharon Yan and Table 87 shows Dr. Yan analyses for the unadjusted mean values for baseline, last visit, and change over that interval for the secondary efficacy endpoints. These results are almost identical to those obtained (Figure 34 for primary endpoint and Figure 37 - Figure 40 for secondary endpoints) using the ANCOVA model with the terms and covariates for the model and confirm the validity of these results and the robust demonstration of efficacy by rasagiline at both 0.5 and 1 mg/day.

Table 86 Mean Total Daily "OFF" Time and Change from Baseline to Treatment Period by Treatment

	Rasagiline 0.5 mg (n=157)	Rasagiline 1 mg (n=142)	Placebo (n=152)
Baseline	6.01 (2.01)	6.25 (2.52)	5.98 (2.23)
Treatment	4.41 (2.65)	4.39 (2.53)	5.19 (2.85)
Change	-1.38 (1.96)	-1.85 (2.03)	-0.88 (1.98)

CLINICAL REVIEW

p-value	0.0199	0.0001
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Table 87 Summary of Secondary Efficacy Results by Treatment Group As Per Statistical Analysis Plan

	0.5 mg	1.0 mg	Placebo
CGE (p-value)	-0.40 .0027	-0.66 .0001	-0.02
ADL at "Off"			
Baseline	15.75	15.54	15.54
Last Visit	15.16	14.86	16.22
Change	-.60	-.68	.68
p-value	.0069	.0034	
Motor at "On"			
Baseline	21.45	20.87	20.81
Last Visit	20.09	19.57	22.02
Change	-1.43	-1.30	1.21
p-value	.0010	.0008	
PD-QUALIF			
Baseline	51.15	50.94	51.76
Last Visit	51.95	52.40	54.86
Change	.80	1.46	3.10
p-value	.0651	.2229	

- Neither the protocol nor Statistical Analysis Plan (SAP) in my reading unequivocally specified how individual diary data would be handled for the analysis of the primary efficacy endpoint (i.e. change from baseline for daily "OFF"). The protocol noted that 3 diaries were to be collected for 3 consecutive days before particular visits. However, there was no specification about precisely when they should be collected. Were they supposed to be collected over 3 consecutive days immediately before the scheduled visit or over a window period such as 3 out of 7 days before the visit? What if they were not collected on 3 consecutive days? The SAP did not specify how the data might be handled if one diary was collected at some relatively distant time before the visit nor defined what time would be considered as "distant." These details are important because results of diaries were to be averaged and one would need to know if one or more diaries collected before a specific visit should have been included in analyses or rejected because they were collected too "early" before the visit. If some diary data were collected too "early" before a scheduled visit what would happen to those data? I asked the sponsor whether specific windows were applied for counting diaries before a visit and not clearly immediately before a scheduled visit or whether they needed to be collected on consecutive days? The sponsor responded that "there were no restrictions regarding the protocol requirement of consecutive diaries or completion time with respect to each visit." However, if more than 3 diaries were collected before a visit, the last 3 diaries were to be included in the efficacy analyses.

Initially, I had questions about whether the sponsor's primary analysis for the primary efficacy endpoint was calculated by simply calculating the mean change from baseline "OFF" time from : 1) "on-treatment" OFF" time derived from the diary data of up to all 9

CLINICAL REVIEW

“on-treatment” diaries that were supposed to be collected in up to 3 diaries before 3 certain visits ; or 2) “on-treatment” OFF” time derived by computing the average for each of 3 periods (and employing LOCF imputation for missing data in a period when there were no diary data collected) and then computing the average of those 3 periods. In response to my specific question about how the primary analysis was conducted, the sponsor confirmed that the “on-treatment” efficacy data were calculated for each patient by computing the average results for each patient based upon the total number of diaries collected during treatment (up to 9 diaries with no more than 3 diaries included prior to each period). In addition, the sponsor informed me that the percentage of diary completion compared to what was expected was very high (89 - 91 %) for all treatment groups and the vast majority of patients completed 9 diaries during treatment. I have discussed the issue of the primary analysis of the primary efficacy endpoint with Dr. Yan who concurs that the primary analysis of the primary efficacy endpoint was conducted appropriately.

- I find it interesting that the sponsor did not amend the protocol with regard to the secondary efficacy endpoints but did change the secondary efficacy endpoints in the Statistical Analysis Plan (SAP). In the SAP (that was supposedly submitted to DNDP approximately 1 month before the blind was broken), the sponsor deleted change from baseline to termination in UPDRS ADL during “ON” state to an additional efficacy endpoint and added two other efficacy endpoints that had been noted as exploratory efficacy endpoints in the protocol. Furthermore, the sponsor outlined a hierarchical sequence for testing secondary efficacy endpoints only when the primary efficacy endpoint was statistically significant (i.e. $p < 0.05$), and required that each secondary endpoint be statistically significant before analyzing the next one according to the sequence in the SAP. Following this change in the SAP, the first three secondary efficacy endpoints outlined in the SAP were statistically significant and the last (fourth one was not significant. However, the original secondary efficacy endpoint that had been deleted as such and relegated to an “additional” efficacy endpoint was not statistically significant. The p value (0.88 by ANCOVA analysis) for the 1 mg/day dose for the change in ADL in the “ON” state did not each approach significance. Nevertheless, both doses of rasagiline appeared to exert a therapeutic effect based upon 3 of the 4 secondary efficacy endpoints identified in the SAP.
- The sponsor did not present subgroup analyses for this study alone but included subgroup analyses for pooled results of both adjunctive studies (PRESTO and LARGO) (Table 85). In those analyses, the sponsor showed that highly statistically ($p < 0.0001$) significant differences were shown for all relevant subgroups (males vs female; < 65 years vs ≥ 65 years) treated with 1 mg/day rasagiline vs placebo. I have also included subgroup analyses conducted by the statistical reviewer, Dr. Yan, for results of only Study PRESTO. These analyses (Table 88) showed that statistically significant differences were observed for the 1 mg/day dose vs placebo for both age categories and that a statistically significant difference was also noted for males. Although the treatment effect of the 1 mg/day dose was not statistically significant for females, the p value approached significance and the likely explanation for the lack of statistical significance is the smaller number (~ half as many males) of females studied compared to males. Numerically the treatment difference for males and females was similar. These analyses suggest that there is no significant differential

CLINICAL REVIEW

response to the beneficial effect of rasagiline with respect to age and gender. There were no analyses with respect to race because most patients were Caucasian.

Table 88 Statistical Reviewer’s Summary and Analyses of Primary Efficacy Endpoint Efficacy Results by Demographic Characteristics

Study/ Protocol #	Primary Endpoint	Variable	Treatment Group				
			Mean (SD)				
			0.5 mg	1 mg	2 mg	Entacap	Placebo
PRESTO (133)	Change in daily "Off"	Gender					
		Male (n=295)	-1.49 (p=.020)	-1.86 (p<.001)			-0.86
		Female (n=156)	-1.12 (p=.658)	-1.92 (p=.129)			-0.96
		Age					
		< 65 (n=237)	-1.35 (p=.127)	-1.49 (p=.030)			-0.86
		≥ 65 (n=214)	-1.42 (p=.188)	-2.33 (p<.001)			-0.90

The sponsor had conducted additional analyses to assess what other category may have changed when patients experienced less “OFF” time. These analyses suggested that much of the time when patients experienced less “OFF” time. These analyses suggested that much of the time no longer spent in “OFF” time was spent in “ON” time without troublesome dyskinesia. This analysis provided a useful perspective to suggest that the much of the loss of time in “OFF” state was not shifted to increased sleep time or “ON” time with were troublesome dyskinesia.

11.2.6. Reviewer’s Conclusions

- Rasagiline showed a therapeutic effect on the primary efficacy outcome measure, change of total “OFF” time from baseline during treatment and indicates that rasagiline is effective as adjunctive therapy in patients with Parkinson's Disease who are experiencing motor fluctuations despite at least LD treatment.
- Both doses (0.5 and 1 mg/day) of rasagiline were therapeutically effective but 1 mg/day showed a numerically greater treatment effect (rasagiline – placebo) that was nearly twice as great as that associated with the lower dose.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- There is a suggestion of efficacy on of rasagiline on some secondary efficacy endpoints. Both doses of rasagiline exerted a statistically significant benefit on the first 3 (Change from Baseline in UPDRS ADL “OFF”, Change from Baseline in UPDRS ADL “OFF”, Change from Baseline in UPDRS Motor “ON”) of 4 secondary efficacy endpoints identified for a hierarchical sequence analysis at an α of 0.05.
- Although the sponsor’s efficacy analyses showed many nominally statistically significant,

CLINICAL REVIEW

beneficial effects of rasagiline on multiple efficacy endpoint in both study phases, I cannot draw serious conclusions about the efficacy on these endpoints because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons.

11.3. Study TVP-1012/122 LARGO (Study Showing Efficacy)

11.3.1. Description of Protocol TVP-1012/133 PRESTO

Title of Study : TVP-1012/122 (LARGO) - A Multicenter, Double Blind, Double Dummy, Randomized, Placebo and Entacapone -Controlled, Parallel Group Study, for the Efficacy, Tolerability and Safety of Rasagiline Mesylate in Levodopa Treated Parkinson's Disease Patients with Motor Fluctuations.

Start : 1/24/01

End: 11/21/02

Protocol Description

The protocol for this study is very similar, although not identical, to the protocol for Study TVP-1012/133 (PRESTO) that was another phase 3, pivotal study also assessing the effect of adjunctive treatment of rasagiline on Parkinson's Disease patients with motor fluctuations despite at least LD therapy. Thus, I have described the major differences between PRESTO and LARGO. Other than these exceptions shown below, the reader can refer to the detailed protocol description for Study TVP-1012/133 (PRESTO) provided in this review.

- LARGO was conducted outside North America in several European countries, Argentina, and Israel. PRESTO was conducted in North America (U.S. and Canada).
- Three parallel study groups in this protocol included placebo, rasagiline 1 mg/day and entacapone (200 mg/each levodopa dose) in a 1:1:1 equal randomization. Double dummy study treatment was used so that all patients tablets of rasagiline or respective placebo or entacapone capsule or respective placebo. PRESTO studied placebo and 1 and 2 mg/day rasagiline.
- The double-blind treatment period was 18 weeks and included a 6 week period in which the LD dosing could be decreased and a 12 week maintenance period in which anti-Parkinson's Disease medications were not to change. PRESTO was conducted with a 26 week double-blind treatment period including a 6 week period during which levodopa could be decreased and an 20 week maintenance period during which anti-Parkinson's Disease medications were not to change.

CLINICAL REVIEW

- All patients participated in a 2 week double-blind double dummy, placebo run-in prior to randomization. PRESTO did not have a double-blind run-in period prior to randomization.
- One inclusion criterion was that patients must be experiencing at least 1 hour daily in the "OFF" state during waking hours. PRESTO required 2.5 hours of daily "OFF" during waking hours.
- One exclusion criterion was patients who had previously used or were presently using entacapone. PRESTO required that patients taking entacapone must have been on a stable dose for at least 14 days prior to baseline.
- The primary efficacy endpoint assess the change from baseline to the treatment period for the mean total daily "OFF" time. Four sets of 3 patient diaries (i.e. 12) were to be averaged during treatment and compared to the mean of 3 diaries at baseline. PRESTO compared the mean total daily "OFF" time from 3 diaries at baseline to the average of 3 sets of 3 patient diaries (i.e. 9) during treatment.
- A secondary efficacy endpoint was the change from baseline to termination visit in the mean total daily "OFF" time measured by home diaries. PRESTO did not include this secondary efficacy endpoint.

Figure 44 shows the schedule of events / assessments for Study TVP-1012/122 (LARGO).

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Figure 44 Schedule of Events / Assessments

	Double Blind Phase						
	Screening	Levodopa Dosage Adjustment			Maintenance Phase		Termination
		Baseline	week 3	week 6	week 10	Week 14	week 18
Day	-28 to 0		±3	±3	±4	±4	±4
Visit #	SC ¹	00	01	02	03	04	05
Informed consent	X						
Inclusion/Exclusion Criteria	X	X (review)					
Medical History	X	X (review)					
Physical/Neurological Exam	X						X
Hoehn & Yahr	X						
SE ADL		X					X
MMSE	X						
Beck Depression	X						X
Chest X-ray	X ¹						
ECG	X						X
Pregnancy Test ²	X ²						X ²
Skin Evaluation	X ³						X
Vital Signs	X	X	X	X	X	X	X
Diary Training	X						
Review Home Diaries (to be completed for 3 days prior to visit)		X		X	X	X	X
UPDRS I, III, IV – “ON”/II – “ON and OFF”)		X			X		X
UPDRS III – OFF ³		X ³					X ³
Clinical Global Evaluation		X					X
Concomitant Therapy	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Dispense Study Medication	Run-in	X	X	X	X	X	
Retrieve Study Medication		Run-in	X	X	X	X	X
Safety Laboratory Tests	X	X	X	X	X	X	X
Investigator’s Signature	X	X	X	X	X	X	X
Study Termination							X
Subject Disposition		X					
AE follow up							X

1. CXR if not completed in last 6 months 2. For women of child-bearing potential only 3. Sub-study at selected sites 4. To be done at screening or at the next scheduled visit, if patient is already enrolled.

Summary of Significant Protocol Amendments

Amendment No.1 : 8/3/00

- Excluded patients who had been treated concomitantly with MAO inhibitors, reserpine, methyl dopa in the 3 months prior to the study, or with anti-emetic or neuroleptic medication with central dopamine antagonist activity in the 6 months prior to the study.
- Modified and further defined the window for study visits from ± 5 days around the actual study visit date to ± 3 days around the actual study visit date for the dosage adjustment phase, and ± 4 days around the maintenance phase.

Amendment No.2 : 10/12/00

- Clarified an inclusion criterion regarding requirement of at least 1 hour of daily “OFF” time during waking hours and confirmation of this with 24 hour diaries in the . Patients enrolled now had to experience motor fluctuations of at least one hour daily in the “OFF” state during the waking hours, not including morning akinesia. These fluctuations should have corresponded to the end of a dose deterioration phenomenon (“wearing off”). This was to be confirmed by the baseline “24-hour” diaries.

CLINICAL REVIEW

- Amended percentage of 3 baseline 24 hour diaries that were supposed to be complete from 80 % to 90 %.

Changes in Statistical Analysis Described in Protocol Compared to Analysis Described in the Statistical Analysis Plan (SAP)

Originally in Protocol : The primary efficacy endpoint was followed by 2 secondary analyses: 1) Change from baseline to each visit in mean total daily “OFF” time (repeated measures analysis) and 2) Categorical change from baseline in mean total daily “OFF” time (responder analysis)

Amended in SAP : These 2 secondary efficacy endpoints were transferred to the “Additional Efficacy Endpoints” section. In addition, the sponsor added Global Improvement by Examiner as a secondary efficacy endpoint. The rationale for this change was to make the list of secondary efficacy endpoints compatible with recommendations of clinical experts based on their importance for the assessment of rasagiline clinical effects. The hierarchical approach was added of specifying an order for analyzing secondary efficacy endpoints was added to control for Type I error.

Many additional efficacy endpoints were added in the SAP “to conform with EMEA guidelines and for exploratory purposes.”

11.3.2. Sponsor’s Presentation of Results of Study TVP-1012/133 PRESTO

Most of the descriptions, summaries, tables, and figures presented here were taken from the sponsor’s electronic submission.

Patient Disposition

A total of 231 subjects entered the rasagiline treatment group, 227 subjects entered the entacapone treatment group, and 229 subjects entered the placebo treatment group (Table 89). From the rasagiline treatment group 208 subjects (90%) completed the full duration of the study and 23 subjects prematurely withdrew from the study. From the entacapone treatment group 197 subjects (87%) completed the study and 30 subjects prematurely withdrew from the study. From the placebo treatment group 194 subjects (85%) completed the study and 35 subjects prematurely withdrew from the study (Table 89). Figure 45 shows the flow of all patients through this study.

CLINICAL REVIEW

Table 89 Patient Disposition

TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Randomized	231	100.0	227	100.0	229	100.0	687	100.0
Prematurely Terminated the Study	23	10.0	30	13.2	35	15.3	88	12.8
Completed the Study	208	90.0	197	86.8	194	84.7	599	87.2

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2

The most common reasons for prematurely withdrawing from the study were subject withdrawal of consent and the experiencing of AEs, each with an overall incidence of 4.9% among all treatment groups (Table 90). The entacapone treatment group had the largest withdrawal AEs (7%). This was followed by the placebo treatment group (5%) and then by the rasagiline treatment group (5%) and then by the entacapone group (7%).

Table 90 Distribution of Termination Reasons

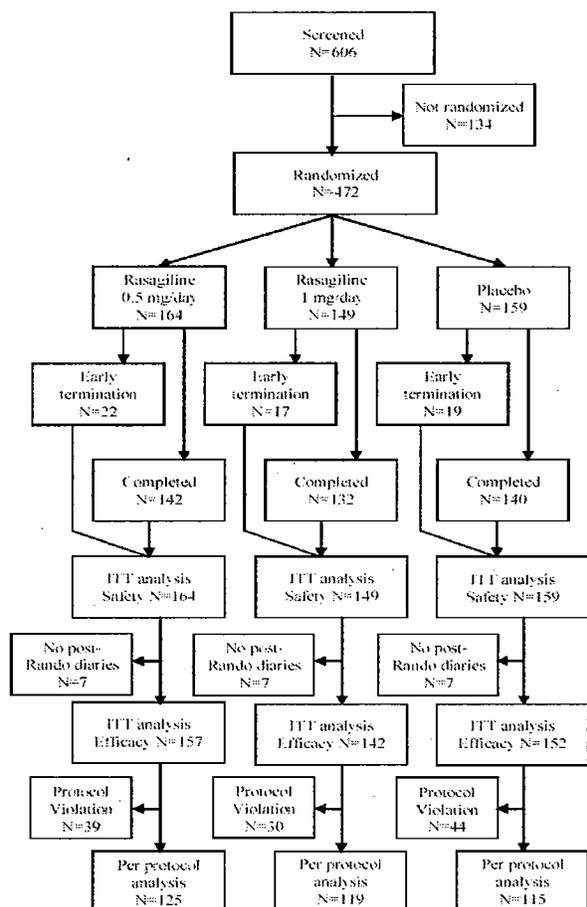
TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Completion According to Protocol	208	90.0	197	86.8	194	84.7	599	87.2
Adverse Experience	7	3.0	16	7.0	11	4.8	34	4.9
Failed to Return	1	0.4	1	0.4	.	.	2	0.3
Subject Withdrew Consent	12	5.2	7	3.1	15	6.6	34	4.9
Investigator's Decision	1	0.4	1	0.4	4	1.7	6	0.9
Sponsor's Decision	.	.	1	0.4	.	.	1	0.1
Initiation of Any Prohibited Treatment	.	.	1	0.4	.	.	1	0.1
Death	2	0.9	3	1.3	4	1.7	9	1.3
Other	1	0.4	1	0.1
All	231	100.0	227	100.0	229	100.0	687	100.0

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2

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Figure 45 Flow Diagram Depicting Progress through Study



Study Conduct and Major Protocol Deviations

On the whole, both patients and investigators complied well with study requirements.

Study Diaries

Nearly all diaries in all treatment groups were considered acceptable (unacceptable = > 5 missing or erroneous entries between 6 a.m and 12 midnight) and evaluable.

Study Drug Compliance

Overall, study drug compliance was relatively good and few patients among the treatment groups were considered to have exhibited poor compliance (i.e. < 70 %).

Major Protocol Deviations

Table 91 represents the incidence of patients with major protocol deviations made during the course of the study. These patients were excluded from the PP cohort. In the rasagiline treatment group there were 34 patients (15%), compared to 43 patients (19%) in the entacapone treatment group and 46 patients (20%) in the placebo treatment group with major protocol violations.

CLINICAL REVIEW

Table 91 Major Protocol Deviations

TVP-1012/133 (PRESTO)	0.5 mg (N=164)		1 mg (N=149)		Placebo (N=159)	
	N	%	N	%	N	%
Description						
Addition of New Anti-PD Medication or Stop of Existing Anti-PD Medication Post Randomization	7	4.26	3	2.01	3	1.88
Change in DA or Other anti-PD Medications Within Less than 30 Days Prior to Randomization	.	.	3	2.01	3	1.88
Increase or Decrease of more than 20% in the Dose of an Existing Anti-PD Medication	5	3.04	5	3.35	8	5.03
Increase or Decrease of more than 20% in the Mean Total Daily LD Dose During Treatment Period After Visit 2	6	3.65	7	4.69	5	3.14
Less than 2 Acceptable Diaries at Baseline	1	0.60
Less than 6 Acceptable Diaries During Treatment	20	12.19	12	8.05	16	10.06
Mean Total Daily OFF time at Baseline of less than 2.5 hours	1	0.60	.	.	2	1.25
Premature Termination from the Study	22	13.41	17	11.4	19	11.94
Study Drug Compliance of Less than 70%	2	1.21	1	0.67	1	0.62
Use of Anti-Emetics and Neuroleptics With Central Dopamine Antagonist Activity Within 6 Months Prior to Randomization or During the Study	.	.	2	1.34	2	1.25
All (At least one Protocol Violation)	39	23.8	30	20.1	44	27.7

Cross-reference: Individual data listing of Protocol Deviations in Appendix 16.2.3.1
 Cross-reference: Individual data listing of Rasagiline Compliance in Appendix 16.2.3.2

Demographics and other Baseline Characteristics

Altogether 687 patients from a total of 11 European countries, Israel and Argentina distributed over 74 study sites underwent randomization. The distribution of subjects by country is displayed in Table 92.

Table 92 Distribution of Patients by Country

TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Argentina	47	20.3	48	21.1	46	20.1	141	20.5
Austria	5	2.2	6	2.6	5	2.2	16	2.3
Belgium	2	0.9	.	.	1	0.4	3	0.4
France	9	3.9	8	3.5	8	3.5	25	3.6
Germany	3	1.3	3	1.3	5	2.2	11	1.6
Hungary	30	13.0	30	13.2	27	11.8	87	12.7
Israel	17	7.4	17	7.5	20	8.7	54	7.9
Italy	45	19.5	49	21.6	47	20.5	141	20.5
Netherlands	9	3.9	9	4.0	7	3.1	25	3.6
Portugal	6	2.6	5	2.2	6	2.6	17	2.5
Romania	34	14.7	34	15.0	36	15.7	104	15.1
Spain	8	3.5	6	2.6	7	3.1	21	3.1
UK	16	6.9	12	5.3	14	6.1	42	6.1
All	231	100.0	227	100.0	229	100.0	687	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4

The great majority (98 – 99 %) of patients from all treatment groups were Caucasian. There were no statistically significant differences in sex between the treatment groups (Table 93).

CLINICAL REVIEW

Table 93 Distribution of Patients by Sex

TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Sex								
Female	77	33.3	88	38.8	97	42.4	262	38.1
Male	154	66.7	139	61.2	132	57.6	425	61.9
All	231	100.0	227	100.0	229	100.0	687	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4

Descriptive statistics for age, and the distribution of subjects by age categories are shown in Table 94. For the 3 treatment groups the mean age was between 63 and 65 years. Approximately 50% of subjects from all treatment groups were equal to or older than 65 years.

Table 94 Distribution of Patients by Age Category

TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Age Category								
54 or Less	40	17.3	45	19.8	31	13.5	116	16.9
55<=Age<65	76	32.9	80	35.2	79	34.5	235	34.2
65<=Age<75	94	40.7	86	37.9	92	40.2	272	39.6
75<=Age	21	9.1	16	7.0	27	11.8	64	9.3
All	231	100.0	227	100.0	229	100.0	687	100.0

Cross-reference: Individual data listing of Demographic Characteristics in Appendix 16.2.4

There were no statistically significant differences between treatment groups with respect to height and weight.

Parkinson's Disease Characteristics

On entry into the study, the treatment groups had a mean PD duration of approximately 9 years. All subjects were on chronic levodopa treatment and a mean LD treatment duration of approximately 7.6 years was obtained for all treatment groups (Table 95). All subjects were experiencing motor fluctuations – all treatment groups had a mean fluctuation duration of approximately 3.3 years (Table 95). There were no statistically significant differences between the treatment groups for these various Parkinson's Disease characteristics.

At baseline, the rasagiline, entacapone and placebo treatment groups were receiving a mean total daily levodopa dose of 722 mg, 706 mg, and 697 mg. There were no statistically significant differences between the treatment groups. The mean number of levodopa daily doses was approximately 5 for all treatment groups.

Treatment groups were not statistically different at baseline with regard to "24-hour" diary parameters (Table 96). The rasagiline treatment group had a mean 16.1 hours of waking time of which 5.6 hours were spent in the "OFF" state and 10.5 hours were spent in the "ON" state. Of

CLINICAL REVIEW

Table 95 Descriptive Statistics of Parkinson's Disease History

TVP-1012/122 (LARGO)		Rasagiline 1 mg	Entacapone	Placebo	All
PD Duration (years)	N	231	227	229	687
	Mean	8.7	9.2	8.8	8.9
	Median	7.9	8.9	7.7	8.1
	Std	4.9	4.7	4.8	4.8
	Min	0.4	0.7	1.5	0.4
	Max	24.2	29.5	27.2	29.5
Levodopa Treatment Duration (years)	N	231	227	229	687
	Mean	7.5	7.6	7.6	7.6
	Median	6.9	6.9	6.8	6.9
	Std	4.6	4.5	4.7	4.6
	Min	0.4	0.5	0.6	0.4
	Max	21.5	23.5	27.2	27.2
Fluctuations Duration (years)	N	231	227	228	686
	Mean	3.3	3.2	3.3	3.3
	Median	2.4	2.5	2.5	2.4
	Std	3.2	2.7	2.8	2.9
	Min	0.1	0.1	0.3	0.1
	Max	21.3	16.5	13.9	21.3
Dyskinesia Duration (years)	N	116	108	127	351
	Mean	3.9	3.6	3.6	3.7
	Median	2.9	2.5	3.1	2.9
	Std	3.5	3.3	2.7	3.1
	Min	0.2	0.2	0.1	0.1
	Max	17.4	16.5	12.5	17.4

Cross-reference: Individual data listing of Parkinson's Disease History in [Appendix 16.2.5](#)

these "ON" hours, 9.1 hours were "ON1" time (i.e., "ON" without dyskinesia or with non-troublesome dyskinesia) and 1.4 hours were "ON2" time (i.e., "ON" with troublesome dyskinesia). The entacapone treatment group had a mean 16 hours of waking time of which 5.6 hours were spent in the "OFF" state and 10.4 hours were spent in the "ON" state. Of these "ON" hours, 9 hours were "ON1" time and 1.4 hours were "ON2" time. The placebo treatment group had a mean 16.1 hours of waking time of which 5.6 hours were spent in the "OFF" state and 10.5 hours were spent in the "ON" state. Of these "ON" hours, 9.1 hours were "ON1" time and 1.4 hours were "ON2" time.

Neither were there any statistically significant differences between the treatment groups at baseline in UPDRS sub-scales and "total" UPDRS scores (i.e. sum of mental, ADL, and motor subscales) (Table 97), in the Severity of Illness scores, in Quality of Life scores, in examiner and subject Schwab and England scores in the "ON" and "OFF" states, in Freezing of Gait scores, and in BECK Depression Inventory scores.

Hoehn and Yahr staging at screening resulted in similar values for all groups with scores of approximately 2.1 and 2.9 units for "ON" and "OFF" states respectively. There were no statistically significant differences between the treatment groups

A mean screening MMSE score of approximately 28.5 units was obtained for all 3 groups.

CLINICAL REVIEW

Table 96 Descriptive Statistics of Baseline "24-Hour" Diary Parameters

TVP-1012/122 (LARGO)		Rasagiline 1 mg	Entacapone	Placebo	All
Mean Total Daily Waking Time (hours) (Baseline)	N	231	227	229	687
	Mean	16.07	16.02	16.05	16.05
	Std	1.66	1.66	1.89	1.74
	Median	16.17	16.00	16.17	16.17
	Min	10.67	11.33	10.17	10.17
	Max	20.33	20.33	21.00	21.00
Mean Total Daily "OFF" Time (hours) (Baseline)	N	231	227	229	687
	Mean	5.58	5.60	5.55	5.57
	Std	2.37	2.59	2.44	2.46
	Median	5.17	5.50	5.17	5.17
	Min	1.33	1.17	1.67	1.17
	Max	13.33	12.83	13.17	13.33
Mean Total Daily "ON" Time (hours) (Baseline)	N	231	227	229	687
	Mean	10.49	10.42	10.50	10.47
	Std	2.46	2.55	2.47	2.49
	Median	10.50	10.50	10.67	10.50
	Min	1.17	1.83	3.33	1.17
	Max	17.50	17.17	16.67	17.50
Mean Total Daily "ON1" Time (hours) (Baseline)	N	231	227	229	687
	Mean	9.10	9.01	9.14	9.08
	Std	2.91	3.30	2.97	3.06
	Median	9.33	9.50	9.33	9.33
	Min	0.00	0.00	0.00	0.00
	Max	15.00	17.17	16.67	17.17
Mean Total Daily "ON2" Time (hours) (Baseline)	N	231	227	229	687
	Mean	1.39	1.41	1.37	1.39
	Std	2.38	2.57	2.27	2.41
	Median	0.00	0.00	0.00	0.00
	Min	0.00	0.00	0.00	0.00
	Max	12.67	13.17	13.00	13.17

Cross-reference: Individual data listing of Derived "24-Hour" Diary Parameters (Baseline, Treatment, Change) in [Appendix 16.2.10.1](#).

CLINICAL REVIEW

Table 97 Descriptive statistics of baseline total and sub-scale UPDRS Scores

TVP-1012/122 (LARGO)		Rasagiline 1 mg	Entacapone	Placebo	All
Total UPDRS (Baseline)	N	231	227	229	687
	Mean	33.64	32.24	33.74	33.21
	Median	31.50	29.50	32.00	31.50
	Std	17.59	16.63	18.81	17.69
	Min	2.00	3.00	2.50	2.00
	Max	95.00	78.50	94.50	95.00
UPDRS Mental (Baseline)	N	231	227	229	687
	Mean	1.90	1.86	1.94	1.90
	Median	2.00	2.00	2.00	2.00
	Std	1.70	1.64	1.77	1.70
	Min	0.00	0.00	0.00	0.00
	Max	8.00	8.00	7.00	8.00
UPDRS ADL "ON" (Baseline)	N	231	227	229	687
	Mean	7.75	7.31	8.11	7.72
	Median	7.00	7.00	7.00	7.00
	Std	5.96	5.27	6.09	5.79
	Min	0.00	0.00	0.00	0.00
	Max	34.00	22.00	28.00	34.00
UPDRS ADL "OFF" (Baseline)	N	231	227	228	686
	Mean	19.03	19.13	18.92	19.03
	Median	18.00	18.00	17.50	18.00
	Std	7.74	7.66	7.61	7.66
	Min	4.00	3.00	2.00	2.00
	Max	44.00	40.00	40.00	44.00
UPDRS Motor "ON" (Baseline)	N	231	227	229	687
	Mean	23.99	23.07	23.69	23.58
	Median	23.00	21.00	22.50	22.00
	Std	12.41	12.34	13.35	12.70
	Min	1.00	2.00	1.00	1.00
	Max	71.00	56.00	65.50	71.00
UPDRS Motor "OFF" (Baseline)	N	38	49	44	131
	Mean	38.72	36.53	40.30	38.43
	Median	38.25	37.00	39.25	37.50
	Std	14.64	16.26	11.90	14.42
	Min	14.50	16.50	15.00	14.50
	Max	78.50	74.50	70.00	78.50
UPDRS Dyskinesia Score (Baseline)	N	231	227	229	687
	Mean	1.42	1.41	1.52	1.45
	Median	0.00	0.00	1.00	1.00
	Std	1.91	1.88	1.84	1.87
	Min	0.00	0.00	0.00	0.00
	Max	9.00	7.00	8.00	9.00

UPDRS Total = UPDRS Mental + UPDRS ADL "ON" + UPDRS Motor "ON"

Cross-reference: Individual data listing of UPDRS Total and Sub-Scale Scores in [Appendix 16.2.10.4](#)

Past and Concomitant Medical Conditions Unrelated to Parkinson's Disease

Subjects entered the study with other medical conditions besides Parkinson's disease. There were no noteworthy differences between the treatment groups.

Concomitant medications that were taken prior to and also during the study period or exclusively during the study period are displayed in Table 98 according to drug class and to drug class and generic name respectively. Approximately 80% of patients from all treatment groups took other PD medications during the study besides their study drug and in addition to their levodopa therapy. The group of PD medications used with the highest incidence (~ 60% in each treatment

CLINICAL REVIEW

group) was the dopamine agonists of which pergolide, followed by pramipexole and then ropinirole were the most commonly used. Amantadine was used with an incidence of approximately 30% in each treatment group. Antimuscarinics were used with the lowest incidence (range of 9 -15%) in each of the 3 treatment groups.

Table 98 Concomitant PD medications by drug or drug group

TVP-1012/122 (LARGO)	Rasagiline 1 mg (N=231)		Entacapone (N=227)		Placebo (N=229)	
	N	%	N	%	N	%
- ALL	175	75.8	175	77.1	175	76.4
AMANTADINE HYDROCHLORIDE	69	29.9	71	31.3	61	26.6
ANTIMUSCARINIC AGENTS	35	15.2	20	8.8	25	10.9
DOPAMIN AGONISTS	141	61.0	135	59.5	130	56.8

Cross-reference: Individual data listing of Concomitant Medications in [Appendix 16.2.8](#)

Primary Efficacy Endpoint - Change from Baseline To Treatment in the Mean Total Daily "OFF" Time

The primary endpoint for this trial was the change from baseline to treatment in the mean total daily "OFF" time.

ITT Cohort

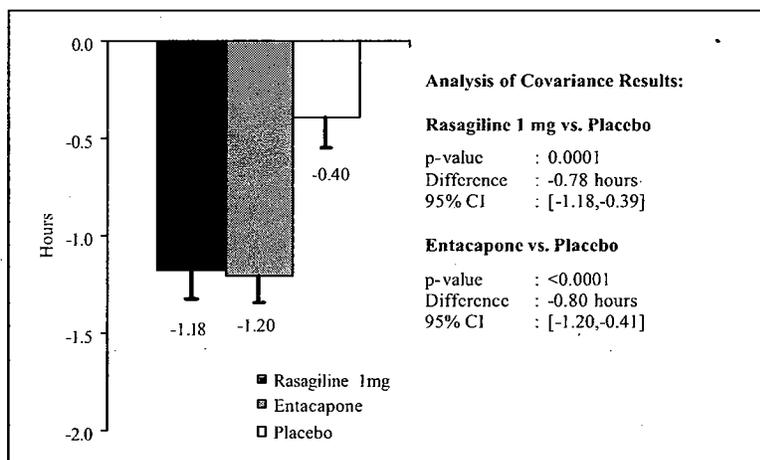
The principal efficacy analysis for this study was the baseline adjusted analysis of covariance for the ITT cohort – represented in Figure 46. The mean baseline total daily "OFF" time for both the rasagiline and entacapone treatment groups was 5.6 hours while for the placebo treatment group it was 5.5 hours. Analysis of Covariance (Figure 46) results in an adjusted mean decrease from baseline in the total daily "OFF" time of 1.18 hours for the rasagiline treatment group, 1.20 hours for the entacapone treatment group and 0.40 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction of 0.78 hours for rasagiline over placebo ($p = 0.0001$). The entacapone versus placebo contrast assessed for validation purpose (Figure 3) reveals a statistically significant effect size of a reduction of 0.80 hours ($p < 0.0001$), comparable with that detected for rasagiline.

Per Protocol (PP) and Completer (CO) Cohorts

The analysis of the primary endpoint conducted for the PP and CO cohorts confirms the results and conclusions of the principal analysis. Descriptive statistics for the PP cohort demonstrate that the mean baseline total daily "OFF" time was 5.6 hours for the rasagiline and entacapone treatment groups and 5.4 hours in the placebo-treated arm. Analysis of Covariance results in an adjusted mean reduction from baseline in the total daily "OFF" time of 1.34 hours for the rasagiline treatment group, 1.43 hours for the entacapone treatment group and 0.62 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction of 0.71 hours for rasagiline over placebo ($p = 0.001$, 95% CI: -1.14 to -0.29). The effect size of entacapone in the PP study cohort is a reduction of 0.80 hours ($p = 0.0003$, 95% CI: -1.23 to -0.37).

CLINICAL REVIEW

Figure 46 Principal Analysis: Adjusted Mean Change from Baseline to Treatment in Total Daily “OFF” Time for ITT Cohort (-SE)



Cross-reference: Statistical Output for “24-Hour” Diary Analyses in [Appendix 16.1.9.4.2](#)

CO Cohort

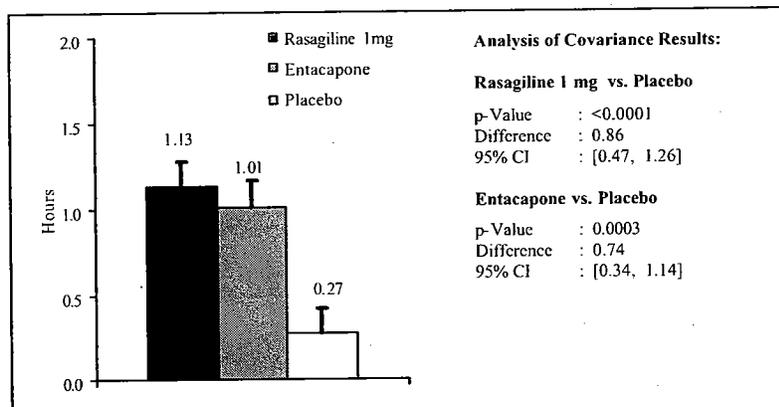
Descriptive statistics for the CO cohort demonstrate that the baseline mean total daily “OFF” time was 5.6 hours for the rasagiline treatment group and 5.5 hours for the entacapone and placebo treatment groups. Analysis of Covariance results in an adjusted mean reduction from baseline in the total daily “OFF” time of 1.29 hours for the rasagiline treatment group, 1.32 hours for the entacapone treatment group and 0.57 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of a reduction of 0.72 hours for rasagiline over placebo ($p = 0.0006$, 95% CI: -1.12 to -0.31). The effect size of entacapone in the CO study cohort is a decrease of 0.75 hours ($p = 0.0004$, 95% CI: -1.16 to -0.34).

Analysis of “ON” and “ON1”

Post-hoc analysis of total daily “ON” (calculated from the sum of “ON1” and “ON2”) and “ON1” and “ON2” times in order to better characterize the reduction of the “OFF” time reveals that the decrease in the total daily “OFF” is mirrored by the increase in the total daily “ON” and “ON1” times. The baseline mean total daily “ON” time was 10.5 hours for the rasagiline and placebo treatment groups and 10.4 hours for the entacapone treatment group. Analysis of Covariance (Figure 47) results in an adjusted mean increase from baseline in the total daily “ON” time of 1.13 hours for the rasagiline treatment group, 1.01 hours for the entacapone treatment group and 0.27 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of an increase of 0.86 hours for rasagiline over placebo ($p < 0.0001$). The effect size of entacapone is an increase of 0.74 hours ($p = 0.0003$).

CLINICAL REVIEW

Figure 47 Adjusted mean change from baseline to treatment in total daily “ON” time for ITT Cohort (\pm SE)

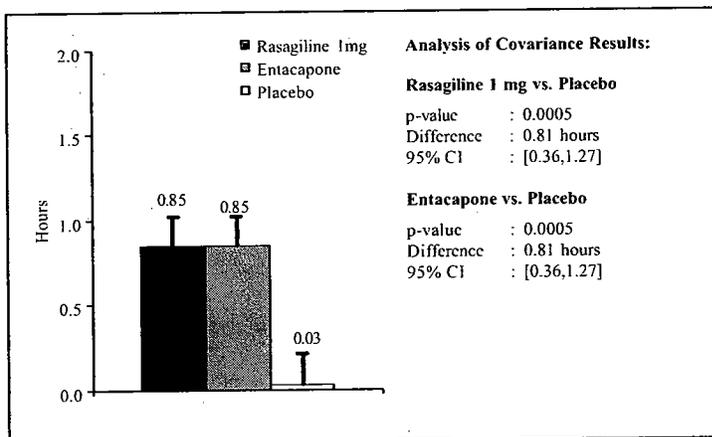


Cross-reference: Statistical Output for “24-Hour” Diary Analyses in [Appendix 16.1.9.4.2](#)

Investigation of whether “ON1” (ON” without dyskinesia or without troublesome dyskinesia) or “ON2” (“ON” with troublesome dyskinesia) contributes to this increase in overall “ON” time reveals that most of the increase in “ON” time is contributed by the increase in “ON1” time. The mean baseline total daily “ON1” time was 9.1 hours for the rasagiline and entacapone treatment groups while for the placebo treatment group it was 9.2 hours.

Analysis of Covariance (Figure 48) results in an adjusted mean increase from baseline in the total daily “ON1” time of 0.85 hours for both the rasagiline and the entacapone treatment groups and of 0.03 hours for the placebo treatment group with an overall statistically significant treatment effect attributed to rasagiline administration of an increase of 0.81 hours for rasagiline over placebo ($p = 0.0005$). The same effect size of 0.81 hours is seen for entacapone over placebo ($p = 0.0005$). There is no statistically significant difference between rasagiline and placebo in the change from baseline in the mean total daily “ON2” time as detailed in the safety section.

Figure 48 Adjusted mean change from baseline to treatment in mean total daily “ON1” time (\pm SE)



Cross-reference: Statistical Output for “24-Hour” Diary Analyses in [Appendix 16.1.9.4.2](#)

CLINICAL REVIEW

Secondary Efficacy Endpoints

The principal analysis of the primary endpoint has demonstrated a highly statistically significant beneficial ($p = 0.0001$) effect for rasagiline treatment. Therefore, in line with the SAP, secondary endpoints could be tested for statistical significance as the experimental error rate of 5% is preserved.

As the analyses performed for the primary endpoint of the study have demonstrated a consistent drug effect across all three subject cohorts, the analyses of secondary and additional efficacy endpoints, in line with the SAP, have been limited to the ITT cohort.

The Hierarchical Approach was also designed to be implemented for controlling the type-I error due to multiple secondary endpoint testing. This approach dictates that secondary endpoints can be tested, at an alpha level of 5%, sequentially in a pre-defined order pending on the significance of the previous endpoint.

The hierarchical order for the 3 secondary endpoints of this study is:

- Global Improvement by the Examiner
- Change from Baseline to Termination in UPDRS ADL During “OFF” state
- Change From Baseline to Termination in UPDRS Motor During “ON” State

This analysis plan was not specified in the protocol nor in protocol amendments but was included in the sponsor’s Statistical Analysis Plan (SAP). The sponsor informed me that the SAP was submitted to FDA/DNDP approximately 1 month before the blind was broken in this study.

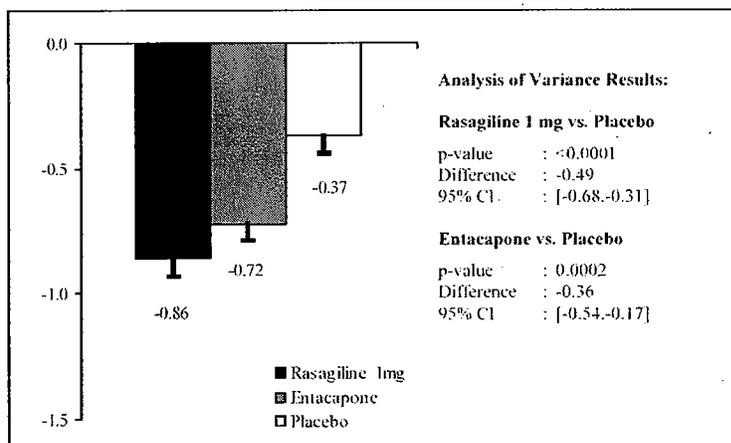
The sponsor did not present statistical analyses for the results for the changes for the secondary efficacy endpoints per se but only presented the statistical results for the ANCOVA model and adjusted means according to the model. The mean results were usually very similar.

Global Improvement by the Examiner at Termination

According to the examiner, by the end of the study the mean values for Global Improvement decreased (i.e., improved) by 0.93 units for the rasagiline treatment group, by 0.79 units for the entacapone treatment group and by 0.44 units for the placebo treatment group. Analysis of Variance (Figure 49) results in an adjusted mean decrease for Global Improvement of 0.86 units for the rasagiline treatment group, 0.72 units for the entacapone treatment group, and 0.37 units for the placebo treatment group with an overall statistically significant treatment effect of a reduction of 0.49 units for rasagiline over placebo ($p < 0.0001$). The effect size of entacapone is a reduction of 0.36 units ($p = 0.0002$, 95% CI: -0.54 to -0.17).

CLINICAL REVIEW

Figure 49 Adjusted mean global improvement by examiner at termination (\pm SE)

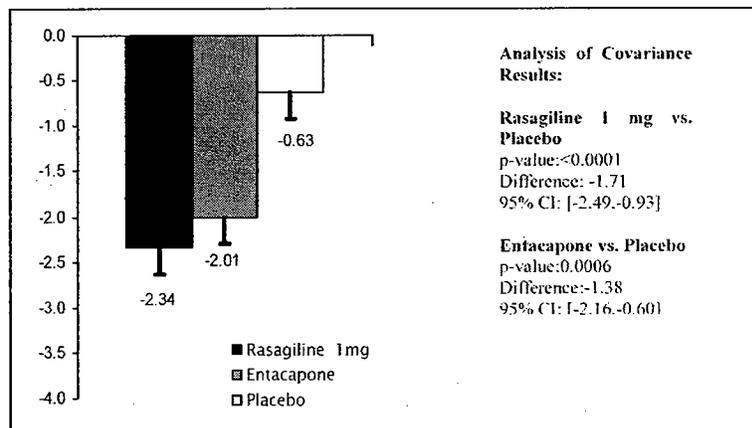


Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

Change from Baseline to Termination in UPDRS ADL During "OFF" State

The mean baseline UPDRS ADL "OFF" was 18.9 units for the rasagiline treatment group, 19.0 units for the entacapone treatment group and 18.8 units for the placebo treatment group. Analysis of Covariance (Figure 50) results in an adjusted mean decrease from baseline to termination in the UPDRS ADL "OFF" of 2.34 units for the rasagiline treatment group, 2.01 units for the entacapone treatment group, and 0.63 units for the placebo treatment group with an overall statistically significant treatment effect of a decrease of 1.71 units for rasagiline over placebo ($p < 0.0001$). The effect size of entacapone is a reduction of 1.38 units ($p = 0.0006$).

Figure 50 Adjusted mean change from baseline in UPDRS ADL "OFF" (\pm SE)



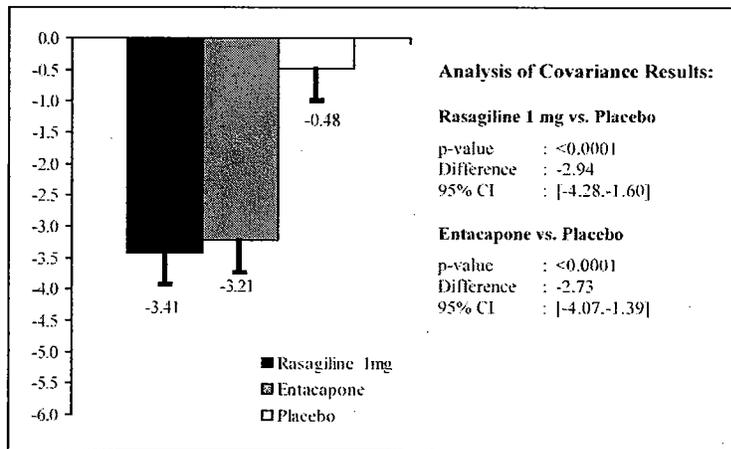
Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in Appendix 16.1.9.4.3.

CLINICAL REVIEW

Change From Baseline to Termination in UPDRS Motor During “ON” State

Mean baseline UPDRS Motor “ON” scores of 23.7 units were obtained for the rasagiline and placebo treatment groups, and of 23 units for the entacapone treatment group. Analysis of Covariance (Figure 51) results in an adjusted mean decrease from baseline to termination in the UPDRS Motor “ON” scores of 3.41 units for the rasagiline treatment group, 3.21 units for the entacapone treatment group, and 0.48 units for the placebo treatment group with an overall statistically significant treatment effect of a decrease of 2.94 units for rasagiline over placebo ($p < 0.0001$). The effect size of entacapone is a reduction of 2.73 units ($p < 0.0001$).

Figure 51 Adjusted mean Change from Baseline to Termination in UPDRS Motor “ON” (\pm SE)



Cross-reference: Statistical Output for Efficacy Analyses besides “24-Hour” Diary Analyses in Appendix 16.1.9.4.3.

Additional Efficacy Endpoints

Several additional efficacy endpoints, some of which had been mentioned in the protocol as exploratory efficacy endpoints, were pre-defined in the SAP and were presented in this report in order to better explore the consistency of the rasagiline effect. In addition, other efficacy endpoints were developed as post-hoc analyses and some were efficacy endpoints in sub-studies. These endpoints were tested at a nominal alpha level of 5%

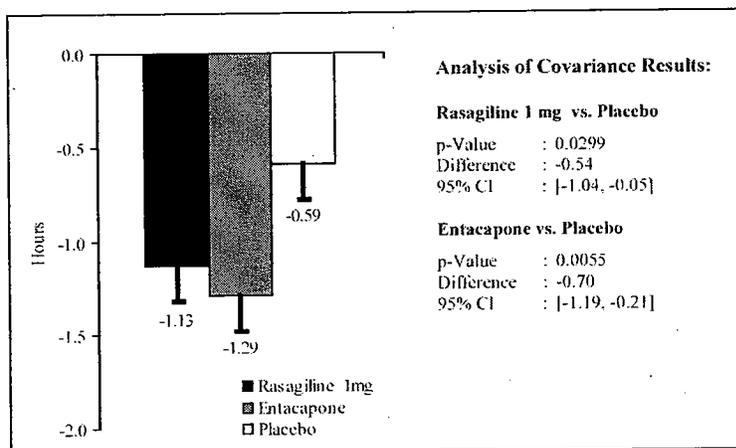
Most of these efficacy endpoints were not considered significant endpoints in the protocol. Thus, I will not present these efficacy data in any detail with the exception of change from baseline for ADL “on”, and change from baseline to termination for total “OFF” that had been identified in the protocol as a secondary efficacy endpoints. However, I will show the treatment effect of 1 mg/day rasagiline in a summary table of many efficacy endpoints predefined in the SAP for this clinical trial (Table 99).

CLINICAL REVIEW

Change from Baseline to Termination in the Mean Total Daily "OFF" Time

A mean baseline total daily "OFF" time of 5.6 hours was obtained for the rasagiline and entacapone treatment group whereas for the placebo treatment group it was 5.5 hours. Analysis of Covariance () results in an adjusted mean decrease from baseline to termination in the mean total daily "OFF" time of 1.13 hours for the rasagiline treatment group, 1.29 hours for the entacapone treatment group, and 0.59 hours for the placebo treatment group with an overall statistically significant treatment effect of a reduction of 0.54 hours for rasagiline over placebo ($p = 0.03$). The effect size of entacapone is a reduction of 0.70 hours ($p = 0.0055$).

Figure 52 Adjusted Mean Change from Baseline to Termination in Total Daily "OFF" Time (\pm SE)



Cross-reference: Statistical Output for "24-Hour" Diary Analyses in Appendix 16.1.9.4.2.

Repeated Measures Analysis of the Change from Baseline to Each Treatment Visit in the Mean Total Daily "OFF" Time

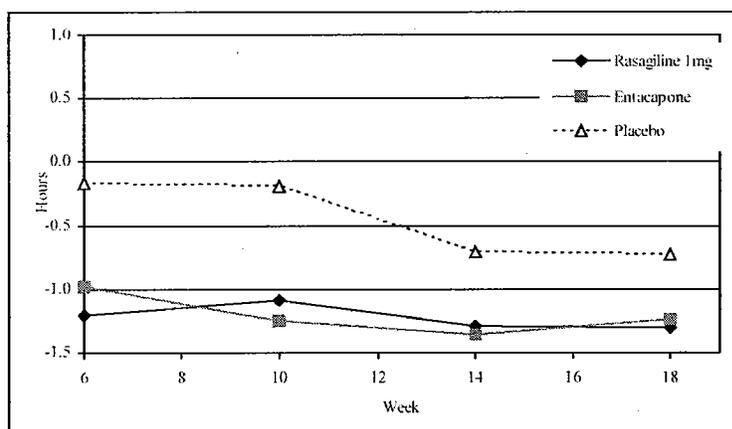
Figure 53 that displays descriptive statistics of mean total daily "OFF" time and the change from baseline by actual week in trial shows that the beneficial effect of rasagiline over placebo (and of entacapone over placebo) is already pronounced by visit 2/week 6, the first post-randomization diary visit. Repeated measures analysis (Figure 53) of baseline adjusted Analysis of Covariance confirms the findings of the primary endpoint of this study by demonstrating that the beneficial effect of rasagiline over placebo is evident across all study visits. The rasagiline versus placebo repeated measures contrast is statistically significant demonstrating that, across visits, the total daily "OFF" time is reduced by 0.82 hours due to rasagiline administration ($p < 0.0001$, 95% CI: -1.21 to -0.43).

A refined assessment of the consistency of the effect size across visits, suggests no statistically significant treatment-by-week interaction ($p = 0.1040$). The repeated measures common slope estimate is -0.02 ($p = 0.0031$) suggesting an extrapolated decrease of approximately 0.24 hours between Week 6 to Week 18, mainly attributed to the placebo arm. The significant beneficial effect is maintained at Week 18 (section 0) for both rasagiline and entacapone treatment groups.

CLINICAL REVIEW

In conclusion, the repeated measures analysis of covariance confirms that the rasagiline effect in reducing the mean total daily “OFF” time is consistent and robust across visits.

Figure 53 Change from baseline to each visit in the mean total daily “OFF” time



Repeated Measures Analysis of Covariance

Time effect was found to be non-significant between groups (p=0.1040)

Parameter	Estimate	P-Value	95% CI	
			Lower	Upper
Common Slope	-0.02	0.0051	-0.04	-0.01
Rasagiline 1mg vs Placebo -Intercept	-0.82	<.0001	-1.21	-0.43
Entacapone vs Placebo -Intercept	-0.82	<.0001	-1.21	-0.42
Rasagiline 1mg vs Entacapone -Intercept	-0.01	0.9671	-0.40	0.38

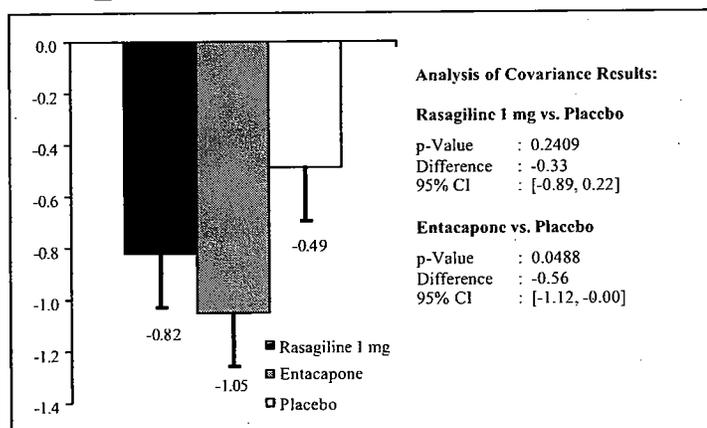
Cross-reference: Statistical Output for “24-Hour” Diary Analyses in Appendix 16.1.9.4.2.

Change from Baseline to Termination in UPDRS ADL During “ON” State

At baseline mean UPDRS ADL “ON” scores of 7.7 units, 7.3 units and 8 units were obtained for the rasagiline, entacapone and placebo treatment groups respectively. Analysis of Covariance (Figure 54) results in an adjusted mean decrease from baseline to termination in the UPDRS ADL “ON” of 0.82 units for the rasagiline treatment group, 1.05 units for the entacapone treatment group and 0.49 units for the placebo treatment group. There is no statistically significant difference between rasagiline and placebo. A borderline treatment effect of a reduction of 0.56 units (p = 0.0488) is evident for entacapone over placebo.

CLINICAL REVIEW

Figure 54 Adjusted mean change from baseline to termination in UPDRS ADL “ON” (\pm SE)



Cross-reference: Statistical Output for Efficacy Analyses besides “24-Hour” Diary Analyses in [Appendix 16.1.9.4.3](#).

Table 99 Summary of Efficacy Endpoints

	Treatment Effect of Rasagiline over Placebo	p value	95% CI
Primary Efficacy Endpoint:			
Change from Baseline to Treatment in Mean Total Daily “OFF” Time			
ITT Cohort	-0.78 hours	p = 0.0001	-1.18 to -0.39
PP Cohort	-0.71 hours	p = 0.001	-1.14 to -0.29
CO Cohort	-0.72 hours	p = 0.0006	-1.12 to -0.31
Secondary Efficacy Endpoints			
Global Improvement by the Examiner at Termination	-0.49 units	p < 0.0001	-0.68 to -0.31
Change from Baseline to Termination in UPDRS ADL During “OFF” State	-1.71 units	p < 0.0001	-2.49 to -0.93
Change From Baseline to Termination in UPDRS Motor During “ON” State	-2.94 units	p < 0.0001	-4.28 to -1.60
Additional Efficacy Endpoints excluding Sub-studies			
Categorical Change from Baseline in the Mean Total Daily “OFF” Time (Responder Analysis)	Odds ratio of 2.5	p < 0.0001	1.62 to 3.85
Change from Baseline to Termination in the Mean Total Daily “OFF” Time	-0.54 hours	p = 0.03	-1.04 to -0.05
Repeated Measures Analysis of the Change from Baseline to Each Treatment Visit in the Mean Total Daily “OFF” Time	-0.82 hours	p < 0.0001	-1.21 to -0.43
Change from Baseline to Termination in UPDRS ADL During “ON” State	-0.33 units	p = 0.2409*	-0.89 to 0.22
Change from Baseline to Termination in Severity of Illness	-0.11 units	p = 0.0378	-0.22 to -0.01
Global Improvement by Subject at Termination	-0.54 units	p < 0.0001	-0.77 to -0.32

CLINICAL REVIEW

	Treatment Effect of Rasagiline 1 mg vs Placebo	P value	95% CI
Change from Baseline to Termination in Examiner Schwab and England ADL "ON" Score	0.93%	p = 0.1794*	-0.43 to 2.29
Change from Baseline to Termination in Examiner Schwab and England ADL "OFF" Score	1.67%	p = 0.0767*	-0.18 to 3.52
Change from Baseline to Termination in Subject Schwab and England ADL "ON" Score	0.73%	p = 0.3684*	-0.86 to 2.33
Change from Baseline to Termination in Subject Schwab and England ADL "OFF"	2.14 %	p = 0.0454	0.04 to 4.25
Change from Baseline in Total Daily Levodopa Dose	-29.76 mg	p = 0.0003	-45.74 to -13.77
Change from Baseline to Termination in Beck Depression Inventory Scale	-0.56 units	p = 0.1274*	-1.29 to 0.16
Additional Efficacy Endpoints including Sub-studies			
Change From Baseline to Termination in UPDRS Motor During "OFF" State	-5.64 units	p = 0.013	-10.06 to -1.22
Change from Baseline to Termination in Quality Of Life (QOL) Score	-2.80 units	p = 0.1362*	-6.48 to 0.89
Change from Baseline to Visit 3/Week 10 in Freezing Of Gate (FOG) Score	-0.69	p = 0.0453	-1.36 to -0.01
Post-Hoc Analyses			
Change from Baseline to Treatment in Mean Total Daily "ON" Time	0.86	p < 0.0001	0.47 to 1.26
Change from Baseline to Treatment in Mean Total Daily "ON]" Time	0.81	p = 0.0005	0.36 to 1.27
Change from Baseline to Termination in Total UPDRS Score	-3.24	p = 0.0003	-5.00 to -1.48
Change from Baseline to Termination in UPDRS Tremor Score	-0.60	p = 0.0022	-0.98 to -0.22
Change from Baseline to Termination in UPDRS Rigidity Score	-0.60	p = 0.0065	-1.03 to -0.17
Change from Baseline to Termination in UPDRS Bradykinesia Score	-1.36	p < 0.0001	-2.01 to -0.72
Change from Baseline to Termination in UPDRS Postural Instability & Gate Disorders (PIGD) Score	-0.31	p = 0.0340	-0.60 to -0.02

* Not statistically significant

Cross-reference: Statistical Output for "24-Hour" Diary Analyses in [Appendix 16.1.9.4.2](#)

Cross-reference: Statistical Output for Efficacy Analyses besides "24-Hour" Diary Analyses in [Appendix 16.1.9.4.3](#)

11.3.3. Sponsor's Discussion of Results of Study TVP-1012/133 PRESTO

The sponsor did not present a discussion of study efficacy results.

11.3.4. Sponsor's Conclusions

The results of this trial demonstrate that daily treatment with 1 mg of rasagiline reduces the total daily "OFF" duration by a mean 0.78 hours in levodopa-treated Parkinson's disease patients with motor fluctuations. This clinically beneficial effect of rasagiline is present across all study

CLINICAL REVIEW

cohorts representing the internal consistency of the data and the adequacy of the conduct of the trial. Furthermore, the highly statistically significant outcome of the principal analysis of this study ($p=0.0001$) has been demonstrated to be conclusive and robust by a variety of alternative and complementary analysis models (Table 99).

This study has also demonstrated the statistically significant beneficial effect of the active study comparator, entacapone 200 mg, administered orally with each levodopa dose, providing additional evidence of the adequacy of the conduct of this clinical trial.

The beneficial effect of rasagiline over placebo is already pronounced at visit 2/week 6, the first post-randomization diary visit, and is evident across all study visits including the termination visit. The clinical relevance of the primary endpoint data is confirmed by the exploratory “responder” analysis, based on the percentages of subjects with an improvement in total daily “OFF” time of at least 60 minutes.

The reduction in the “OFF” time is mirrored by the increase in the total daily “ON” and “ON1” times and is not accompanied by an increase in unwanted troublesome dyskinesia. Analyses of the secondary endpoints that were adjusted for multiplicity have demonstrated an overall statistically significant treatment effect that can be attributed to rasagiline treatment for all 3 secondary endpoints: Global Improvement by the Examiner, UPDRS ADL in “OFF” state, and UPDRS Motor in the “ON” state. The fact that the UPDRS Motor score is improved in the “ON” state with rasagiline treatment in patients who previously had been optimized on levodopa therapy may suggest that rasagiline does not only extend the duration of levodopa benefit but may also enhance its maximal antiparkinsonian effect.

A statistically significant treatment effect of rasagiline over placebo has been seen regarding Changes in the Severity of Illness, the Freezing of Gait, and the Subject Schwab and England ADL “OFF” scores. Improvements due to rasagiline treatment seen for the different PD “OFF” scores including the UPDRS Motor score during “OFF” can be seen as a reduction in the severity of a patient’s “OFF”. The similarity between results obtained in the examiner and subject Global Improvement scores provides additional reinforcement of confidence in results obtained for this endpoint placed at the top of the hierarchy of the secondary endpoints.

Post-hoc analyses have revealed statistically significant differences between rasagiline and placebo for the Total UPDRS score and for other items from the UPDRS representing the 4 cardinal features of Parkinson’s disease: tremor, rigidity, bradykinesia and postural instability. Rasagiline treatment has also shown a slight but statistically significant decrease in the mean total daily levodopa dose. A similar decrease is seen for entacapone treatment. Larger reductions in the daily levodopa dose following entacapone treatment have been seen in previous studies in which reductions were permitted according to the design of the study. This study did not permit the reduction except in the case of intolerability during the first 6 weeks of the study. It may be speculated that a more flexible study design could lead to a larger levodopa-sparing effect for both active groups.

There were no statistically significant differences between the rasagiline and placebo treatment groups regarding changes in the UPDRS ADL “ON”, Quality of Life, Examiner Schwab and

CLINICAL REVIEW

England ADL “ON” and “OFF” and Subject Schwab and England ADL “ON”, and in the Beck Depression scores.

11.3.5. Reviewer’s Comments

- The sponsor did not present nor discuss results of the unadjusted mean values for the primary efficacy endpoint nor for the secondary efficacy endpoints. Table 100 shows results for the unadjusted mean change of the primary efficacy endpoint for all treatment groups based upon the analyses of the statistical reviewer, Dr. Sharon Yan and Table 101 shows Dr. Yan’s analyses for the unadjusted mean values for baseline, last visit, and change over that interval for the secondary efficacy endpoints. These results are almost identical to those obtained (Figure 46 for primary endpoint and Figure 49 - Figure 51 for secondary endpoints) using the ANCOVA model with the terms and covariates for the model and confirm the validity of these results and the robust demonstration of efficacy by rasagiline at 1 mg/day.

Table 100 Mean Total Daily “OFF” Time and Change from Baseline During Treatment by Treatment Group

	Rasagiline 1 mg (n=222)	Entacapone (n=218)	Placebo (n=218)
Baseline	5.58 (2.38)	5.58 (2.56)	5.54 (2.45)
Treatment	4.41 (2.65)	4.39 (2.53)	5.19 (2.85)
Change	-1.17 (2.16)	-1.19 (2.19)	-.35 (2.46)
p-value	.0001	.0001	

Table 101 Summary of Secondary Efficacy Results by Treatment Group as Outlined in the Statistical Analysis Plan

	Rasagiline 1 mg (n=222)	Entacapone (n=220)	Placebo (n=218)
CGE (p-value)	-.93 <0.001	-.79 <0.001	-.44
ADL at "Off"			
Baseline	18.95	19.04	18.71
Last Visit	16.34	16.76	17.82
Change	-2.61	-2.28	-.89
p-value	.0001	.0012	
Motor at "On"			
Baseline	23.78	23.00	23.54
Last Visit	19.91	19.49	22.72
Change	-3.87	-3.51	-.82
p-value	.0001	.0006	

- Neither the protocol nor Statistical Analysis Plan (SAP) specified how individual diary data would be handled for the analysis of the primary efficacy endpoint (i.e. change from baseline for daily “OFF”). The protocol noted that 3 diaries were to be collected for 3

CLINICAL REVIEW

consecutive days before particular visits. However, there was no specification about precisely when they should be collected. Were they supposed to be collected over 3 consecutive days immediately before the scheduled visit or over a window period such as 3 out of 7 days before the visit? What if they were not collected on 3 consecutive days? The SAP did not specify how the data might be handled if one diary was collected at some relatively distant time before the visit nor defined what time would be considered as “distant.” These details are important because results of diaries were to be averaged and one would need to know if one or more diaries collected before a specific visit should have been included in analyses or rejected because they were collected too “early” before the visit. If some diary data were collected too “early” before a scheduled visit what would happen to those data? I asked the sponsor whether specific windows were applied for counting diaries before a visit and not clearly immediately before a scheduled visit or whether they needed to be collected on consecutive days? The sponsor responded that “there were no restrictions regarding the protocol requirement of consecutive diaries or completion time with respect to each visit.”

Initially, I had questions about whether the sponsor’s primary analysis for the primary efficacy endpoint was calculated by simply calculating the mean change from baseline “OFF” time from : 1) “on-treatment” OFF” time derived from the diary data of up to all 12 “on-treatment” diaries that were supposed to be collected in up to 3 diaries before 4 certain visits ; or 2) “on-treatment” OFF” time derived by computing the average for each of 4 periods (and employing LOCF imputation for missing data in a period when there were no diary data collected) and then computing the average of those 4 periods. In response to my specific question about how the primary analysis was conducted, the sponsor confirmed that the “on-treatment” efficacy data were calculated for each patient by computing the average results for each patient based upon the total number of diaries collected during treatment (up to 12 diaries with no more than 3 diaries included prior to each period). In addition, the sponsor informed me that the percentage of diary completion compared to what was expected was very high (97 -98 %) for all treatment groups and the vast majority of patients completed 12 diaries during treatment. I have discussed the issue of the primary analysis of the primary efficacy endpoint with Dr. Yan who concurs that the primary analysis of the primary efficacy endpoint was conducted appropriately.

- Similarly as with adjunctive Study PRESTO, I find it interesting that the sponsor did not amend the protocol with regard to the secondary efficacy endpoints but did change the secondary efficacy endpoints in the Statistical Analysis Plan (SAP). In the SAP (that was supposedly submitted to DNDP approximately 1 month before the blind was broken), the sponsor deleted change from baseline to termination in UPDRS ADL during “ON” state and change from baseline to termination for total daily “OFF” time from secondary efficacy endpoints in the protocol to and made them additional efficacy endpoints. The sponsor also added one efficacy endpoint (global improvement by the examiner at termination) that had been noted as exploratory efficacy endpoint in the protocol as a secondary efficacy endpoint in the SAP. Furthermore, the sponsor outlined a hierarchical sequence for testing secondary efficacy endpoints only when the primary efficacy endpoint was statistically significant (i.e. $p < 0.05$), and required that each secondary endpoint be statistically significant before analyzing the next one according to the sequence in the SAP. Following this change in the SAP, all three secondary efficacy endpoints outlined in the SAP were statistically significant.

CLINICAL REVIEW

One original secondary efficacy endpoint (change from baseline to termination for total daily “OFF” time) that had been deleted as such and relegated to an “additional” efficacy endpoint was statistically significant and another (change from baseline to termination for ADL during “ON”) similarly relegated to an additional efficacy endpoint was not significant.

- The sponsor did not present subgroup analyses for this study alone but included subgroup analyses for pooled results of both adjunctive studies (PRESTO and LARGO) (Table 85). In those analyses, the sponsor showed that highly statistically ($P < 0.0001$) significant differences were shown for all relevant subgroups (males vs female; < 65 years vs ≥ 65 years) treated with 1 mg/day rasagiline vs placebo. I have also included subgroup analyses conducted by the statistical reviewer, Dr. Yan. These analyses (Table 88) showed that statistically significant differences were observed for the 1 mg/day dose vs placebo for both males and females and that a statistically significant difference was also noted only for patients ≥ 65 years. Patients < 65 years did not show a statistically significant results vs placebo as they did in the other adjunctive treatment study (PRESTO). The reason a statistically significant benefit from 1 mg/day rasagiline did not occur is not clear. The number of patients in each age group was similar. These analyses suggest that there is no significant differential response to the beneficial effect of rasagiline with respect to age but contrasts with the benefit observed for both categories in PRESTO. Overall, I do not have any reason to be concerned that patients < 65 can experience therapeutic benefit from 1 mg/day rasagiline as adjunctive treatment. There were no analyses with respect to race because most patients were Caucasian.

Table 102 Statistical Reviewer’s Summary and Analyses of Primary Efficacy Endpoint Efficacy Results by Demographic Characteristics

Study/ Protocol #	Primary Endpoint	Variable	Treatment Group				
			0.5 mg	1 mg	2 mg	Entacap	Placebo
LARGO (122)	Change in daily "Off"	Gender					
		Male (n=414)		-1.26 (p=.025)		-1.27 (p=.024)	-0.58
		Female (n=244)		-0.97 (p=.021)		-1.06 (p=.003)	-0.02
		Age					
		< 65 (312)		-0.94 (p=.236)		-1.31 (p=.017)	-0.56
		≥ 65 (n=346)		-1.37 (p<.001)		-1.08 (p=.002)	-0.18

- The sponsor had conducted additional analyses to assess what other category may have changed when patients experienced less “OFF” time. These analyses suggested that much of the time no longer spent in “OFF” time was spent in “ON” time without troublesome dyskinesia. This analysis provided a useful perspective to suggest that the loss of time in “OFF” state was not shifted to increased sleep time or “ON” time with were troublesome dyskinesia.

CLINICAL REVIEW

- It is noteworthy that the protocol proposed 150 patients per treatment group and 450 total patients. The protocol also provided for an interim analysis to assess the sample size number. This analysis was conducted using pooled variability of all treatment groups together. (I was told treatment groups were not analyzed according to groups A, B, and C and assessed). The results suggested that the study was underpowered and additional patients (~ 80/ treatment group or ~ 240 total) were enrolled to meet the size estimates. This increase in planned enrollment increased the sample size by ~ 50 %. Despite the fact the safety data were being pooled and periodically reviewed by a Safety Data Monitoring Board periodically according to treatment groups shown as A,B, or C (without specification of actual treatment), I have been told that the blind had not been broken and efficacy data was not reviewed according to these grouping categories. I reviewed the coefficient of variation-CV (SD/mean) for the primary efficacy endpoint (change from baseline during treatment for total "OFF" time) in each of the adjunctive studies (PRESTO and LARGO). It is interesting to note that the mean CV for the PRESTO study for 1 mg/day rasagiline and placebo was ~ 168 % and the corresponding mean for the LARGO study was ~ 444 %. Thus, it seems that there was much more variability in results for this primary efficacy endpoint in the LARGO study, possibly because it was conducted outside North America (e.g. many European countries, Argentina, and Israel). It is not too unusual to note differences in studies conducted in North America compared to sites outside of North America.

11.3.6. Reviewer's Conclusions

- Rasagiline (1 mg/day) showed a therapeutic effect on the primary efficacy outcome measure, change of total "OFF" time from baseline during treatment and indicates that rasagiline is effective as adjunctive therapy in patients with Parkinson's Disease who are experiencing motor fluctuations despite at least LD treatment.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- There is a suggestion of efficacy on of rasagiline on some secondary efficacy endpoints. Both doses of rasagiline exerted a statistically significant benefit on the first 3 (Change from Baseline in UPDRS ADL "OFF", Change from Baseline in UPDRS ADL "OFF", Change from Baseline in UPDRS Motor "ON") of 4 secondary efficacy endpoints identified for a hierarchical sequence analysis at an α of 0.05.
- Although the sponsor's efficacy analyses showed many nominally statistically significant, beneficial effects of rasagiline on multiple efficacy endpoint in both study phases, I cannot draw serious conclusions about the efficacy on these endpoints because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons.
- Although there was no formal comparison of the efficacy of rasagiline with entacapone (both of which were investigated in this study), in general the benefit of rasagiline in general appeared to be similar to that of entacapone.

CLINICAL REVIEW

12. LABELING ISSUES

I have reviewed the Clinical Studies, Indication and Usage, Dosing and Administration, and Tyramine / rasagiline interaction sections of the label and have the following comments/concerns related to major or significant labeling issues.

Clinical Studies

- I recommend deleting the presentation of any efficacy data that are not relevant to the primary analyses of the primary efficacy endpoints for the 3 pivotal trials.
- I recommend presenting the actual primary efficacy endpoint data for all 3 pivotal trials and have deleting data
- I recommend clarifying that the primary efficacy endpoint for both adjunctive treatment trials involved calculating the post-treatment data collected at various, specified times throughout these trials.
- I recommend noting in the Conclusions of the Adjunctive Studies that the 0.5 mg dose was effective and that the beneficial result was numerically less than that observed with the 1 mg rasagiline dose.

Indication and Usage

- I recommend only minor wording changes.

Dosing and Administration

- I have recommended dosing for monotherapy (no LD) in Parkinson's Disease patients as 1 mg daily.
- I have recommended initiating dosing for adjunctive therapy (with LD) in all Parkinson's Disease patients (including those with hepatic impairment as 0.5 mg daily, and assessing the response after 1 week treatment to see if the dose is well tolerated. If the 0.5 mg dose is tolerated and the patient is experiencing motor fluctuations, the dose should be increased to 1 mg daily.

Tyramine / Rasagiline Interaction

I have recommended that this section be revised and completed after the sponsor has conducted additional tyramine studies prior to approval. The data derived from these studies should be incorporated into this section.

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

/s/

Leonard Kapcala
6/29/04 08:24:29 PM
MEDICAL OFFICER

John, Here is my review for your signature. Please
let me know if any questions. Len

John Feeney
7/1/04 03:37:17 PM
MEDICAL OFFICER
Concur; see my memo to the file.

MEMORANDUM

NDA 21-641 Agilect (Rasagiline Mesylate)

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

SUBJECT: Original NDA for the Treatment of Parkinson's Disease

DATE: June 14, 2004

Background

The sponsor has proposed the use of rasagiline 1mg/day as monotherapy for the treatment of early Parkinson's disease and as an adjunct to L-dopa in advanced Parkinson's disease. The sponsor has submitted the results from 3 efficacy trials to support approval. In addition, the sponsor has submitted an integrated safety summary, with particular attention directed to 1) tyramine sensitivity and 2) the occurrence of melanoma during the development of rasagiline.

Rasagiline is an MAO-B inhibitor with a structure similar to selegiline. In contrast to selegiline, rasagiline is not metabolized to amphetamine or methamphetamine. It is rapidly metabolized to aminoindan.

The following reviews have addressed different aspects of this NDA:

Statistical Review	Sharon Yan, Ph.D.
Clinical Safety Review	M. Lisa Jones, M.D., M.P.H.
Safety Team Leader Memorandum	Judith Racoosin, M.D.
Efficacy Review/Tyramine Studies	Leonard Kapcala, M.D.
Pharm/Tox Review	Paul Roney, Ph.D.
Biopharmaceutics Review	Andre Jackson, Ph.D.
Chemistry Review	William Timmer, Ph.D.
Clinical Site Inspections/DSI (GCP)	Ni Khin, M.D.
Foreign Site Inspection/DSI (GLP)	Jacqueline O'Shaughnessy, Ph.D.
DMETS (Medication Errors)	Linda Wisniewski, R.N.

Dr. Racoosin has provided a concise summary of the overall safety profile of rasagiline. Therefore, this report will focus on: 1) overall efficacy, 2) tyramine sensitivity (risk of "cheese reaction"), and 3) melanoma.

Efficacy

Early Parkinson's Disease; TEMPO (232)

The efficacy of Agilect in the treatment of early Parkinson's disease was demonstrated in one large randomized, double-blind, placebo-controlled, parallel group study, TEMPO. This was a multicenter study conducted in the US and Canada, with almost 90% of patients enrolled at US centers. In this trial, patients with PD diagnosed within the past year were randomized to rasagiline 2mg, rasagiline 1mg, or placebo. Patients were followed for 6 months or until they required the addition of dopaminergic medications for their symptoms. Patients were allowed to use anticholinergics at any time during the trial if needed.

Patient flow for analysis purposes was as follows:

	Rasagiline 1mg	Rasagiline 2mg	Placebo
Total randomized	134	132	138
Need for additional therapy for PD	15	22	23
Discontinuations:			
Adverse event	5	1	1
Failed to return	1	0	0
Subject request	2	2	2
Poor response	0	1	0
Other	0	1	0

The primary outcome measure was the UPDRS total score at the six month visit (or the LOCF if patients dropped out prematurely or required dopaminergic medications earlier than 6 months). The primary analysis was an ANCOVA comparing the change from baseline for each of the drug groups versus placebo. The results were adjusted for the multiple comparisons.

The results on the UPDRS total score at the last visit were as follows:

	<u>UPDRS mean (mean change from baseline)</u>
Rasagiline 1mg	24.75 (0.06), p=0.0001
Rasagiline 2mg	26.61 (0.72), p=0.0001
Placebo	28.44 (3.91)

While the changes from baseline were comparable for the two rasagiline dose groups, the change was numerically slightly in favor of the 1mg group.

Exploratory secondary analyses were performed, but a pre-specified analysis plan to adjust for multiple comparisons was not provided.

Advanced Parkinson's Disease; PRESTO (133)

The sponsor performed 2 studies in patients with advanced PD, PRESTO and LARGO. PRESTO was a randomized, placebo-controlled, parallel-group study comparing rasagiline 0.5mg, rasagiline 1mg, and placebo added onto a regimen including L-dopa. PRESTO was a North American study conducted in the U.S. and Canada. The double-blind period lasted 26 weeks. The primary outcome measure was change from baseline in daily OFF time.

The primary analysis was an ANCOVA with an adjustment for the two dose comparisons to placebo. Secondary outcomes included a global measure, the UPDRS subscales, and a quality of life measure. A hierarchical statistical approach to the secondary measures was planned.

A total of 472 patients were randomized to the 3 treatment groups. The mean daily OFF time was about 6 hours for each group. The mean decrease in OFF time was 0.9 hours for the placebo group, 1.4 hours for the 0.5mg group, and 1.8 hours for the 1mg group. The comparisons of the rasagiline groups to placebo were both highly statistically significant.

The results for the 7-point global improvement scale were also statistically significant for each of the rasagiline comparisons, although the mean scores for each of the rasagiline groups only fell between "no change" and "minimally improved."

On the UPDRS ADL subscale (measured during an OFF period), the mean score was about 15 for each group. After treatment, each rasagiline group improved by about 0.6 while the placebo group worsened by about 0.6. These comparisons were also statistically significant.

On the UPDRS Motor subscale (measured during an ON period), the mean score was about 21 for each group. After treatment, each rasagiline group improved by about 1.3 while the placebo group worsened by about 1.2. These comparisons were statistically significant.

On the QOL scale, the total score could range from 0-128. At baseline, the mean scores were 51 for the treatment groups. After treatment, the placebo group had a mean worsening of 3 while the rasagiline groups had a mean worsening from 1-1.5. The differences were not statistically significant.

Advanced Parkinson's Disease; LARGO (122)

LARGO was a randomized, placebo-controlled, parallel-group study comparing rasagiline 1mg, entacapone, and placebo added on to a regimen including L-dopa. LARGO was a foreign study conducted in Europe, Argentina, and Israel. The double-

blind period lasted 18 weeks. The primary outcome measure was change from baseline in daily OFF time.

The primary analysis was an ANCOVA. Secondary outcomes included a global measure, the UPDRS subscales, and a quality of life measure. A hierarchical statistical approach to the secondary measures was planned.

A total of 687 patients were randomized to the 3 treatment groups. The mean daily OFF time was about 5.5 hours for each group. The mean decrease in OFF time was 0.3 hours for the placebo group, 1.2 hours for the 1mg rasagiline group, and 1.2 hours for the entacapone group. The comparisons of the rasagiline group to placebo was highly statistically significant.

The results for the 7-point global improvement scale was also statistically significant for the rasagiline comparison.

On the UPDRS ADL subscale (measured during an OFF period), the mean score was about 19 for each group. After treatment, the rasagiline group improved by about 2.6 while the placebo group only improved by about 0.9. This comparison was also statistically significant.

On the UPDRS Motor subscale (measured during an ON period), the mean score was about 23 for each group. After treatment, the rasagiline group improved by about 3.9 while the placebo group improved by about 0.8. This comparison was statistically significant.

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Tyramine Sensitivity

While the sponsor has studied rasagiline doses to include 2mg/day, the proposed marketing dose is only 1mg/day both as initial monotherapy and as later adjunctive therapy with L-dopa. The sponsor has presented the results of 4 studies which assess the selectivity of rasagiline for MAO-B. Dr.Kapcala has reviewed all 4 studies. He believes that Study P94159 is the best assessment of tyramine sensitivity. At the same time, he believes there are significant problems with the study and there is a "definite need for better quantitative characterization of the extent of MAO-A inhibition."

1. Study P94159 (Paris)

This was a tyramine challenge study conducted in young, healthy male volunteers roughly ten years ago. There were 3 sequential cohorts of 9 subjects each. In each cohort, subjects were randomized in a 2:1 ratio to active drug or placebo (6 active and 3 placebo). The 3 active drugs were rasagiline 1mg, rasagiline 2mg, and selegiline 10mg. Every subject in each cohort was treated with placebo for 10 days and on days 8, 9, and 10 underwent tyramine challenges at escalating doses to define a baseline tyramine sensitivity. Then the subjects were treated with their randomized treatment for 10 days with repeat tyramine testing on the last 3 days. The new tyramine threshold was determined and compared to the threshold at baseline.

A fourth cohort, rasagiline 3mg, was planned but apparently not studied.

The responses to standard tyramine challenges in this study were measured in two ways: the TYR 30 and the TYR 30 ratio. The TYR 30 is the dose of tyramine that caused a BP elevation of at least 30mmHg. The TYR 30 ratio is the TYR 30 after exposure to placebo during baseline divided by the TYR 30 after exposure to study drug, a measure of altered tyramine sensitivity within the same subject. The standard doses of tyramine administered in this study were: 50mg, 100mg, 200mg, 400mg, and 800mg. With exposure to placebo, the TYR 30 was usually 400mg, 800mg, or was undetermined because tyramine doses greater than 800mg were not administered.

Six subjects were exposed to rasagiline 1mg. At this dose, none demonstrated a TYR 30 of 200mg or less. Likewise, at this dose, none showed an alteration in tyramine sensitivity compared to their experience on placebo.

Six subjects were exposed to rasagiline 2mg. At this dose, 2 subjects had a TYR 30 of 200mg and the other 4 had TYR 30s of 400mg. All showed evidence of increased sensitivity to tyramine compared to their experience on placebo.

One possible limitation of this study is that it only assessed tyramine sensitivity after 7-10 days of dosing with rasagiline and did not assess the time course of MAO-A inhibition with chronic dosing. Information on tyramine sensitivity after chronic dosing with rasagiline could come from the tyramine sub-studies of the controlled trials described below.

Dr.Kapcala describes some problems with the Paris study.

First, he is concerned about the potency of the tyramine used, because a number of subjects were insensitive to the tyramine, even at doses of 800mg. It is unusual not to see thresholds around 400-500mg of tyramine at baseline.

Second, the study only included young, healthy males. Dr.Kapcala believes a study in older subjects, including both men and women, should be performed. The sample sizes per group were also very small.

Third, the site inspection raised some questions about the completeness of record keeping. The clock times of particular blood pressure measurements were not recorded. While this is true, the BP measurements were performed and recorded in sequence and this does not appear to raise serious doubts about the results.

Finally, it is worth noting that Dr.Kapcala found the study report fairly difficult to follow, given that the endpoint reported was a "clinical endpoint," which was not described in the protocol and varied from the per protocol endpoint. Blood pressure changes alone were easier to interpret.

2. Study 132 (Pennsylvania)

This was a tyramine challenge study performed at the Pennsylvania Hospital between 1998 and 2000. By design, there were 2 sequential cohorts of 9 patients each. Within each cohort, patients were randomized to active drug (n=6) or placebo (n=3) and then challenged with tyramine. In the first cohort, patients were treated with rasagiline 1mg/day or placebo. In the second cohort, undertaken after the first cohort, patients were treated with rasagiline 2mg/day or placebo.

During screening, all patients were challenged with 75mg tyramine. After randomization, patients were treated with study drug for 3 weeks and then admitted to an in-patient study unit for intensive BP monitoring. On day 22, patients were challenged with 25mg tyramine. On day 23, patients were challenged with 50mg tyramine. On day 24, patients were challenged with 75mg tyramine. The patients were then discharged and continued treatment for the next 7 weeks. Then they returned to the study unit for a 75mg tyramine challenge.

By protocol, patients were to take tyramine capsules along with a morning meal. In practice, they all received the tyramine in applesauce, followed 5-10 minutes later by the morning meal.

The inclusion/exclusion criteria stipulated that patients have Parkinson's disease and be treated with a stable dose of L-dopa. Other concomitant PD medications were also allowed.

Dropouts prior to day 24 were to be replaced. From Dr. Kapcala's review, there was one dropout each in the 1mg (patient 105) and the 2mg (patient 206) groups.

There were no tyramine reactions in the placebo and 1mg groups. There were 2 tyramine reactions in the 2mg group (patients 206 and 209). Neither patient with a tyramine reaction needed intervention and both resolved spontaneously within 1-2 hours.

Two other patients had potentially clinically significant vital sign changes (patient 104 in the 1mg group and patient 208 in the 2mg group); both experienced low blood pressure.

The sponsor maintains that because the tyramine was given before the morning meal, under fasting conditions, there would have been rapid absorption and increased bioavailability. Dr. Kapcala does not agree. He expressed concern that the approach used in this study may not be sensitive enough to demonstrate a change in tyramine sensitivity. He believes that the approach "...must be validated before one could make any interpretations about changes in tyramine sensitivity (and MAO-A inhibition) related to the presence or absence of blood pressure responses to tyramine in these studies."

In tyramine challenge studies reviewed by DNDP in recent years, patients are usually challenged with increasing doses of tyramine (up to 800mg) during baseline to establish each patient's tyramine threshold for a SBP rise of 30mmHg. Then, with study drug on board, the patient is challenged again to determine the new tyramine threshold. In this approach, each patient serves as their own control and even small changes in tyramine sensitivity can be determined. The Paris study followed this design. Study 132 was not designed to determine a change in sensitivity in this more familiar way. Study 132 was designed to establish that rasagiline did not put patients at risk for a tyramine reaction from a standardized tyramine challenge (which was hopefully comparable to a high-tyramine meal).

A relevant question is whether the 75mg tyramine challenge (under the conditions of administration) was comparable to a high-tyramine meal. Dr. Kapcala has shown in his review that the bioavailability of tyramine administered as a capsule can be markedly affected by whether it is taken in a fed or fasted state. Even if the bioavailability is reduced in the fed state, I do not believe that fact alone invalidates Study 132. The sponsor can be asked to show that the plasma concentrations of tyramine from a high-tyramine meal are comparable to those observed after 75mg as administered in Study 132. I expect that the 75mg challenge from Study 132 can be shown to provide coverage for a high-tyramine meal, but I agree with Dr. Kapcala that this has not been demonstrated.

If the 75mg challenge in Study 132 is shown to be ecologically valid, I still find the following limitations in the study. Safe passage in 6 patients at rasagiline 1mg is not enough to reassure, especially when the next dose of rasagiline tested (2mg) was associated with a tyramine response in 2/6 patients. Note also that the two rasagiline dose groups were not randomized groups. Thus, absent randomization and given the

small sample size per group (n=6), there could have been confounding factors not equally distributed across the dose groups, blurring any interpretation of the results.

3. PRESTO Tyramine Sub-Study (133)

PRESTO was a randomized placebo-controlled trial in which patients with advanced PD treated with L-dopa were randomized to rasagiline 0.5mg/day, rasagiline 1.0mg/day, or placebo. In this tyramine sub-study, 55 patients completing the 6-month treatment period of PRESTO were challenged with **50mg** tyramine administered immediately at the end of a meal, added to one of several dairy desserts.

There were 22 patients in the placebo group, 22 in the 0.5mg group, and 13 in the 1mg group. Of these, 4 patients experienced increases in SBP of > 30mmHg for at least 3 consecutive measurements, as shown below.

	Placebo	0.5mg/day	1.0mg/day
Number Studied	22	22	13
Tyramine Reactions	1	3	0

Two other placebo patients had 30mmHg increases in SBP for 2 consecutive measurements.

One of the three 0.5mg/day rasagiline patients represented in the table above had the BP elevations coincident with an OFF period complicating the interpretation of the event. For one of the other two 0.5mg/day patients, the staff believed the results were driven by a transiently low baseline BP measurement. The third patient's BP peaked at 200/95 from a baseline of 124/70. None of the patients required intervention to treat the BP elevations.

The sponsor points to the occurrence of tyramine reactions in placebo patients and the lack of tyramine reactions in the 1mg/day group to support the MAO-B selectivity of rasagiline. Dr. Kapcala believes the method of administration of tyramine in this study (immediately after a meal and with variable desserts) would contribute to variability and would confound the interpretation of any results. Given the tyramine reactions observed at 0.5mg/day, I would certainly not view the PRESTO sub-study as strengthening the sponsor's case for selectivity. Note that the dose of tyramine was only 50mg in this study, lower than in the next study to be described.

4. TEMPO Tyramine Sub-Study (232)

TEMPO was a randomized placebo-controlled trial in which patients with early PD not treated with L-dopa were randomized to rasagiline 1mg/day, rasagiline 2mg/day, or placebo. In this tyramine sub-study, 55 patients completing the 6-month treatment period of TEMPO were challenged with **75mg** tyramine administered 30 minutes after a meal, mixed with applesauce.

There were 17 patients in the placebo group, 19 in the 1mg group, and 19 in the 2mg group. Of these, 2 patients experienced increases in SBP approaching 30mmHg which the Safety Monitoring Committee considered possible tyramine interactions, as shown below.

	Placebo	1mg/day	2mg/day
Number Studied	17	19	19
Tyramine Reactions	0	0	2

None of the patients required intervention to treat the BP elevations.

The sponsor points to the lack of tyramine reactions in the 1mg/day group to support the MAO-B selectivity of rasagiline at that dose. Dr. Kapcala believes the method of administration of tyramine in this study would confound the interpretation of any results. I believe the results of the TEMPO sub-study address my concern about the small sample sizes in Study 132; i.e. the number of patients with safe passage at 1mg/day is increased to 38 (6 from Study 132, 19 from the TEMPO sub-study, and 13 from the PRESTO sub-study).

Overall Assessment of Tyramine Studies

The sponsor has not made a strong case for the selectivity of rasagiline 1mg/day for MAO-B. The sensitivity of the Paris study is questionable given that many volunteers had no detectable tyramine threshold, even when tested at 800mg of tyramine in a fasted state. This brings into question the potency of the tyramine used for the Paris study. I believe the Pennsylvania study (Study 132) might have had adequate sensitivity, but the sponsor should confirm this by providing data on tyramine levels or tyramine sensitivities when a high-tyramine meal and the 75mg challenge used in Study 132 are compared. Similar data should be provided bearing on the tyramine challenges used in the TEMPO and PRESTO sub-studies.

In the PRESTO sub-study, at least one patient treated with 0.5mg/day seemed to have a convincing tyramine reaction (which did not require intervention); several other cases in the 0.5mg/day group were harder to interpret. This does not provide reassurance for a daily dose of 1mg.

In the TEMPO sub-study, 2 possible tyramine reactions in the 2mg/day group occurred. None were observed in the 1mg/day group.

There is an additional issue bearing on the tyramine results across all studies. Early in development, the sponsor chose to perform separate tyramine studies for patients with and without concomitant L-dopa. While those studies (Paris and Pennsylvania) *might* signal the safety of a daily dose of 1mg without tyramine dietary restrictions, the 2 sub-studies provide contradictory results. With a signal of increased tyramine sensitivity at

0.5mg/day in the PRESTO study (tyramine dose of 50mg) but safe passage at 1mg/day in the TEMPO study (tyramine dose of 75mg), one possible explanation for the discrepant results might be heightened sensitivity in the face of concomitant L-dopa (as used in the PRESTO study). An adequate pharmacokinetic explanation for this possible interaction has not been forthcoming, but a pharmacodynamic explanation cannot be ruled out. This issue merits further consideration.

I agree with Dr.Kapcala that the best approach at this point would be to perform a formal tyramine sensitivity study (with a similar design to the Paris study) investigating 20 newly diagnosed PD patients in each of the following arms: placebo, 0.5mg rasagiline, 1mg rasagiline, and 2mg rasagiline. It may even be helpful to have a 3mg rasagiline arm in the study. Half the patients (10) in each group should be on concomitant L-dopa with study drug; the other half should be on study drug alone. The patients should be newly diagnosed to avoid confounding by the use of other drugs for PD.

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Melanoma

By early-2001, there had been 5 reports of melanoma during the development of rasagiline (2 invasive and 3 in situ). All 5 of the cases had occurred in North America and all were in patients on active drug. At that time, the sponsor, along with their expert consultants, met with DNDP to discuss plans for continued development of rasagiline. It was agreed that more careful screening for melanoma should be instituted while patients were informed about the cases that had already occurred.

Three Controlled Trials (PRESTO, LARGO, TEMPO)

In PRESTO, North American patients with advanced PD who were treated with concomitant L-dopa were randomized equally to 3 groups: placebo, 0.5mg rasagiline, or 1.0mg rasagiline. Active dermatologic screening was in place throughout the trial. The double-blind controlled trial lasted about 6 months and was followed by a 6-month active controlled extension study. In the extension study, patients originally treated with placebo were equally randomized to either 0.5mg or 1.0mg of rasagiline; other patients continued on their same regimen. In the placebo-controlled trial, active screening was employed with the following results:

	Placebo	Rasagiline 0.5mg	Rasagiline 1.0mg
Number randomized	159	164	149
Number of melanomas	0	1	2

If we consider 4 groups of patients through the end of the active extension study, diagnosed melanomas were as follows:

	Placebo, then 0.5mg	Placebo, then 1.0mg	Rasagiline 0.5mg	Rasagiline 1.0mg
Number of melanomas*	0	1	2	4

* Cumulative number across both placebo-controlled and active-controlled phases

In PRESTO (including the 6-month active extension) a direct comparison of number of melanomas in patients treated with active drug for the full year (6/313) versus number of melanomas in patients with a 6-month delay to active treatment (1/159) yielded a p-value of 0.43 (Fishers Exact Test).

In LARGO, a non-North American study, patients with advanced PD who were treated with concomitant L-dopa were randomized equally to placebo, rasagiline 1.0mg, or entacapone. The double-blind controlled trial lasted about 4-5 months and was followed by a 9-month active controlled extension study. In the extension study, patients originally treated with placebo were switched to 1.0mg of rasagiline; other patients continued on their same regimen. In the placebo-controlled trial, active screening was employed with the following results:

	Placebo	Rasagiline 1.0mg
Number randomized	229	231
Number of melanomas	1	0

In the active extension of LARGO, no melanomas were reported.

TEMPO was a North American study that enrolled patients with early PD, not on concomitant L-dopa. The controlled trial lasted 6 months and was followed by a 6-month active-control extension. Patients were randomized to placebo, rasagiline 1.0mg, or rasagiline 2.0mg. In the extension study, patients originally treated with placebo were switched to 2.0mg of rasagiline. Active screening for melanoma was begun during the conduct of TEMPO. The distribution of melanomas in the placebo-controlled portion of TEMPO was as follows:

	Placebo	Rasagiline 1.0mg	Rasagiline 2.0mg
Number randomized	138	134	132
Number of melanomas	0	0	1

If we consider 4 groups in the active extension of TEMPO, the distribution of melanomas was as follows:

	Placebo, then 2.0mg	Rasagiline 1.0mg	Rasagiline 2.0mg
Number of melanomas*	0	0	2

* Cumulative number across both placebo-controlled and active-controlled phases

SEER

In the U.S., a registry, the Surveillance, Epidemiology, and End Results (SEER), is run by the National Cancer Institute and collects data on newly reported cases of cancer, to include melanoma. Case ascertainment in SEER is thought to be very good for cases of invasive melanoma and perhaps less reliable for cases of melanoma in situ. Therefore, SEER calculates melanoma incidence only for invasive melanoma. Based on the number of patient-years exposure to rasagiline in early 2001 (any dose), the expected number of cases of invasive melanoma was 0.392 using SEER data. The observed number for invasive melanoma was 2 yielding an Observed/Expected Ratio of 5.10 (95% CI 0.6-18.4). As discussed by Dr. Jones, it might be reasonable to assume 25% under-reporting in SEER; correcting for this would result in an Observed/Expected Ratio of **4.1 (95% CI 0.5-15)** for that time.

While Dr. Jones has updated the comparison to SEER through recent times, the sponsor has argued that this may be an unfair comparison because active dermatologic screening in rasagiline-treated patients occurred after 2001 and is not part of the SEER program. That may be true, but I wonder if screening is as critical a determinant when the analysis is limited to *invasive* melanoma as it is when the analysis also includes *in situ* melanoma. [Recall that the comparisons to SEER only include invasive melanomas for the reasons discussed above.] In any case, the updated rasagiline data includes 7 cases of invasive melanoma (one was diagnosed after 2.5 months on drug) for an Observed/Expected Ratio of **5.4 (95% CI 2.2-11)**, assuming 50% under-reporting in SEER.

Increased Risk of Melanoma in Parkinson's Disease

A possible increased risk with rasagiline when compared to the SEER data could potentially be attributable to an increased risk in patients with Parkinson's disease. Dr. Jones describes six lines of evidence supporting an increased risk of melanoma in Parkinson's disease patients. The sponsor performed two studies, one in Israel and one in both Israel and North America. In each, patients with PD were recruited and carefully screened for melanoma. The results were then compared to incidence figures in the comparable background populations. For the first study in Israel, it is not clear to me that the comparison group underwent comparable dermatologic screening. For the second study, in Israel and North America, whether the results suggested an increase or a decrease in risk depended on which comparator study was used. One comparison of the North American data to a cohort limited to Massachusetts suggested a 10-fold increase in patients with PD. A simple comparison of the same North American data to an American Academy of Dermatology screening program in the general population (described in more detail later) suggested no difference. [It might be informative to repeat this last analysis adjusting for age and gender.]

Dr. Jones also describes a study by Jansson and Jankovic (1985). This was a retrospective study of 400 medical charts of patients with PD. The authors found a low

overall cancer rate (relative risk 0.3), but an increased rate of melanoma (relative risk 6). Dr. Jones also describes a study by Moller et al (1995). The authors identified 7046 PD patients by reviewing inpatient records from 1977 to 1989. Information on cancer incidence was then obtained through 1990 in the Danish cancer registry. There was an increased risk for melanoma (relative risk 1.96).

TEVA recently commissioned a continuation of the Moller study through 1998. The cohort was increase to roughly 14,000 PD patients. For these patients, the standardized incidence ratio (SIR) was about 2.

The sixth study, performed by the sponsor, is poorly described in the NDA. Further information will be requested from the sponsor. Basically, the sponsor compiled a cohort of 919 U.S. patients with a history of melanoma and a control group of 862 age-gender matched controls. The prevalence of P.D. was 2.9% in the melanoma cohort and 1.3% in controls. The sponsor presents this study to support an increased risk of PD in patients with melanoma.

The Parkinson's Study Group Comparison

A direct comparison with a PD cohort was also performed in 2001. A cohort of Parkinson's disease patients (similarly without active dermatologic screening) was assembled from 3 PD studies conducted by the Parkinson's Study Group (PSG), an independent group of PD investigators. Across the 3 studies, there were 1296 patient-years of exposure among PD patients and 3 cases of melanoma were recognized. The incidence density for rasagiline (based on the original 5 cases), 5.8 per 1000 PYs, compared to this PSG incidence density, 2.3 per 1000 PYs, yielded a ratio of 2.5 (95% CI 0.6-10.5).

Active Dermatologic Screening

After discussions between the sponsor and DNDP in early 2001, it was agreed that continued development of rasagiline required careful surveillance for melanoma every 3 months at a minimum. As increased screening began, the number of recognized melanomas almost immediately doubled. Several more cases were captured over time. Ultimately, a total of 16 cases of melanoma were identified in 15 rasagiline-treated patients. One melanoma case was identified in a placebo-treated patient. And 3 other melanoma cases were diagnosed before treatment initiation.

Better identification of cases through closer monitoring presented a new challenge for data analysis beyond the original 5 identified cases. No longer could comparisons be made to prevalence and incidence figures compiled through registries without careful dermatologic screening programs.

To address this problem, the DNDP safety team pursued data from an American Academy of Dermatology melanoma screening project. In that project, community members were solicited to join a voluntary screening project through public service announcements in the local media. A total of 242,374 subjects were screened and prevalence figures calculated by age and gender. These figures were compared to a subgroup of all rasagiline patients (those in North America who were actively screened and for whom risk factor data was available, roughly 600 patients). The results are presented in Dr. Jones' safety review, Table 63, and are shown below.

Invasive Melanoma				In Situ Melanoma			
Observed	Expected	Obs/Exp	95% CI	Observed	Expected	Obs/Exp	95% CI
4	1.5	2.6	0.7-6.7	6	0.6	10.2	3.7-22

The 10-fold increase for in situ melanomas seems particularly troubling, given the comparable dermatologic screening for the two groups. [I would also expect, like Dr. Jones, that the people most likely to respond to the AAD public service announcements would be people who thought of themselves as "at risk," perhaps because of fair complexion, sun exposure, or family history. This has the potential to inflate the expected number and reduce the Observed/Expected ratio.] It seems unlikely that such an increase in risk could be explained by the presence of Parkinson's disease alone.

In active dermatologic screening programs, different from the SEER registry, the distinction between in situ and invasive melanoma is probably artificial. Only minor histologic differences may distinguish between the two cancer types. Therefore, for the AAD/rasagiline comparisons above, invasive melanoma and in situ melanoma might better be considered together. If we do this, the number observed is 10 while the expected is 2.1, with an Observed/Expected Ratio of **4.7 (95% CI: 2.3-8.7)**.

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Other Parkinson's Drug Development Programs (without active dermatologic screening)

The DNDP safety group looked across 4 other PD drug development projects for comparative data. The results of that investigation are shown below. These numbers include all melanomas, in situ and invasive.

	Total Subjects	Total Person-Yrs	Number of Cases of Melanoma	Number of Melanomas per Total N	Incidence Density per 1000 PYs
Pramipexole	5881	6909	11	0.19	1.6
Ropinirole	3138	3377	1	0.03	0.3
Entacapone	2202	2486	0	NA	NA
Tolcapone	2847	3200	33	1.16	10.3
Rasagiline	1935	2450	20	1.03	8.2*

* Had been 5.8 per 1000 PYs pre-active screening

Tolcapone and rasagiline both have an excess of cases. I reviewed Dr. Tresley's original FDA safety review for tolcapone and found reference to only one skin cancer (Table, p68 of his review). Thus, the occurrence of melanoma did not affect the approvability of the application at that time. Obviously, the issue of melanoma with tolcapone will be pursued further by DNDP.

In addition to the above information compiled by the DNDP Safety Team, there is experience from two recent NDAs for drug products for PD. Apokyn was recently approved to treat "Off" periods in the later stages of PD. Among 550 patients treated with Apokyn (535 pt-yrs), there were 2 cases of melanoma observed. Zelapar (Zydis selegiline) is being developed for PD. Among 578 patients treated with Zelapar (perhaps 500 pt-yrs), there was 1 case of melanoma observed.

Transdermal selegiline is currently being developed for depression. Studies in that development project have included patients with a variety of psychiatric diagnoses. Among 2,761 patients treated in Phase 2/3 trials, no melanomas were reported.

Melanoma Discussion

The rasagiline development project can be divided into two time periods for purposes of melanoma analyses, pre- and post-screening initiation. Because the SEER database does not provide incidence data for melanoma in situ, data on melanoma in situ and invasive melanoma can be analyzed separately. The table below shows the Observed/Expected Ratios for rasagiline versus relevant comparator groups. None of these particular comparator groups are PD populations.

	In Situ	Invasive
Pre-Active Screening	---	4* (95%CI:0.5-15)
With Active Screening	10** (95%CI: 3.7-22)	2.6** (95%CI: 0.7-7)
	In Situ and Invasive Combined	
With Active Screening	4.7** (95%CI: 2.3-8.7)	

* Using SEER as comparison group and assuming 25% under-reporting for SEER

** Using AAD screening project as comparison group

Both SEER and the AAD screening project include subjects from the general population, not a population restricted exclusively to PD patients. A question then is: could a possible excess of cases for rasagiline (if not due to chance) be attributed to an increased incidence of melanoma in patients with PD? The answer appears to be no.

From Dr. Jones' safety review, it appears reasonable to assume a 2-fold excess in patients with PD compared to the general population, based on the relative risk noted in the Moller et al study. Therefore, the excess for melanoma (O/E Ratio of 4.7) is difficult to explain by Parkinson's disease alone.

A direct comparison of melanoma incidence (both in situ and invasive, combined) in the rasagiline program (pre-active screening) to the incidence in the PSG studies yielded an incidence density ratio of 2.5, although the 95% confidence interval included 1.0 (0.6-10.5).

At the times of approval for marketing, no other PD drug discussed above was recognized as having an incidence density for melanoma that matched or exceeded that for rasagiline (8.2 per 1000 PYs), even using the incidence density pre-active screening (5.8 per 1000 PYs). At the time of approval for tolcapone, only 1 case of skin cancer was discussed in the FDA safety review; the newly reported figure of 33 melanomas, with an incidence density of 10.3 per 1000 PYs, needs further investigation. The recently approved Apokyn had an incidence density of about 4, but this was based on a very small (given Apokyn's status as a priority drug for an unapproved indication in PD), entirely North American (with that associated risk) safety database.

In summary, all sources of data used in the above comparisons trend in the wrong direction to suggest an increased incidence of melanoma in the rasagiline safety database. Two comparisons are statistically significant: 1) melanoma data with rasagiline/AAD, and 2) updated invasive melanoma data with rasagiline/SEER. Because the strongest safety signal might arise from the in situ comparison using the AAD screening project, it is worth noting some details of the 6 rasagiline in situ cases used for that comparison. In particular, 4 of the 6 rasagiline cases were captured with active screening between 5-9 months after starting rasagiline. The biological plausibility of in situ melanomas arising due to drug within that time frame might be a subject of further debate.

Suggested Further Analysis for Melanoma

In the 2 pivotal studies, TEMPO and PRESTO, patients completing the placebo-controlled phase were switched to rasagiline and followed forward in time. In the safety database, this created a cohort of patients for whom treatment with rasagiline was artificially delayed for up to 6 months. It would be interesting to see a comparison of the incidence and timing of melanoma between this delayed group and the non-delayed patients, including all follow-up time in open-label extension studies, to see if any differences emerge. I would not include LARGO in the analysis because of the general under-reporting of adverse events in that study and because it did not include North American patients.

Also, it seems relevant to investigate the risk of melanoma in PD patients further. The sponsor performed an active screening program in PD patients in North America. An active screening program of the general background population in North America has been conducted by the AAD. As mentioned above, the simple comparison between these two groups (which suggests no difference in melanoma risk) should be refined, adjusting for age and gender.

Melanoma Conclusions

At this time, the sponsor has not provided convincing evidence that the incidence density for all melanomas (in situ and invasive) observed during the rasagiline development project can be dismissed as a spurious finding. The incidence density pre-active screening was 5.8 per 1000PYs. This exceeds that seen in the PSG comparison group, although the difference is not statistically significant. Further, under active screening, the number of observed lesions was significantly greater than that seen in the AAD screening project. While the sponsor has presented data supporting a case for a higher incidence of melanoma in patients with PD, it seems unlikely that the excess with rasagiline can all be reasonably attributed to such an excess risk in PD. Suggestions for further analyses are provided above.

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Overall Conclusions

The sponsor has provided evidence to support the efficacy of rasagiline 1mg/day in the treatment of early and advanced Parkinson's disease.

There is evidence to suggest that rasagiline at a dose of 2mg/day may no longer be selective for MAO-B; this could lead to possible clinical sequelae. At the same time, the tyramine sensitivity of patients treated with rasagiline 1mg/day may not yet be adequately characterized. Therefore, a further tyramine challenge study is recommended, incorporating some of the ideas described above. [For labeling, concomitant medications that inhibit CYP1A2 have the potential to increase exposure to rasagiline and increase tyramine sensitivity.]

The relatively high incidence density for melanoma observed during rasagiline development deserves further consideration. At this point in time, it cannot be dismissed as a spurious finding.

Recommendations

An Approvable Letter should be sent requesting that the sponsor further address the above concerns about tyramine sensitivity and the risk of melanoma.

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/s/

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