

Long-term Outcome of Early Versus Delayed Rasagiline Treatment in Early Parkinson's Disease

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Abstract: The purpose of this study was to compare the long-term clinical outcome of early versus delayed rasagiline treatment in early Parkinson's disease (PD). Subjects (N = 404) were randomly assigned to initial treatment with rasagiline (early-start group) or placebo for 6 months followed by rasagiline (delayed-start group) in the TEMPO study. Subjects who chose to participate in an open-label extension (N = 306) continued to receive rasagiline as well as other PD medications as needed. Average (\pm SD) duration in the study was 3.6 ± 2.1 years; 177 subjects received rasagiline for ≥ 5.0 years. Over the entire 6.5-year follow-up period, the adjusted mean difference in change from baseline in total UPDRS scores was 2.5 units (SE 1.1; $P = 0.021$) or 16% (SE 5.7; $P = 0.006$) in favor of the early-start versus

delayed-start rasagiline group. Although the interaction between treatment and time was significant, values for the early-start group were better than the delayed-start group across all time points. Significantly less worsening (percent change) in total UPDRS scores was observed in the early-start group at the time points 0.5, 1.5, 2.0, 3.0, 4.5, 5.0, and 5.5 years ($P < 0.05$). Compared to delayed start, early initiation of rasagiline provided long-term clinical benefit, even in the face of treatment with other dopaminergic agents. This might reflect enduring benefits due to neuroprotection or effects on compensatory mechanisms in early PD. © 2008 Movement Disorder Society

Key words: rasagiline; Parkinson's disease; treatment; neuroprotection; disease modification; MAO-B inhibitor

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Rasagiline (*N*-propargyl-1[*R*]-aminoindan) mesylate (TVP-1012) is a selective irreversible inhibitor of monoamine oxidase type B (MAO-B).¹ It provides symptomatic benefit both as monotherapy in early Parkinson's disease (PD)² and as an adjunct to levodopa in moderate to advanced disease.^{3,4} In addition, rasagiline provides a neuroprotective effect in a variety of cell culture and animal models.⁵⁻¹²

In the rasagiline TVP-1012 in *Early Monotherapy for Parkinson's disease Outpatients* (TEMPO) study, 404 subjects with early PD were randomly assigned to receive blinded treatment with rasagiline 1 mg/day for 1 year, 2 mg/day for 1 year, or placebo for 6 months followed by rasagiline 2 mg/day for 6 months. At the end of the 6-month placebo-controlled phase of the study, the effect size for change in total Unified Parkinson's Disease Rating Scale (UPDRS) scores was 4.20 units in favor of rasagiline 1 mg/day versus placebo ($P < 0.001$) and 3.56 in favor of rasagiline 2 mg/day versus placebo ($P < 0.001$). At the end of 12 months, subjects treated with rasagiline 1 mg/day or 2 mg/day for 1 year had a 1.82- and 2.29-unit smaller increase (less worsening) in total UPDRS score when compared with subjects treated with placebo for 6 months followed by rasagiline 2 mg/day for 6 months ($P = 0.05$ and $P = 0.01$).¹³ These results indicated that the benefit of rasagiline at 1 year could not be fully explained by a simple symptomatic mechanism and suggested the possibility that rasagiline might slow clinical progression of the disease.

The current report describes results of the long-term open-label extension of the TEMPO study in which subjects were treated with rasagiline for up to 6.5 years. The goal of this study was to compare long-term clinical progression of the disease as assessed by total UPDRS scores in the early-start versus delayed-start groups.

PATIENTS AND METHODS

Study Population

To be eligible to enter the TEMPO study, subjects had to be older than 35 years, have PD confirmed by the presence of two of three cardinal signs (resting tremor, bradykinesia, rigidity), and be Hoehn and Yahr stage I through III. At enrollment, subjects could be receiving stable dosages of anticholinergic medications, but other PD medications were not permitted. Stable dosages of the antidepressants amitriptyline, paroxetine, sertraline, fluvoxamine, and trazodone were permitted. Subjects who required additional dopaminergic

therapy during the 6-month double-blind phase were entered into the active treatment phase and received blinded treatment with rasagiline. Those who required additional symptomatic therapy in the active treatment phase, despite blinded treatment with rasagiline, were treated with a dopamine agonist or carbidopa/levodopa as an adjunct to rasagiline. Subjects who completed the 52-week double-blind TEMPO study were eligible to enter the open-label extension. Investigators and patients remained blinded to the original assignment (early vs. delayed).

Subjects were enrolled into the TEMPO study at 32 participating study centers in the United States and Canada from November 1997 through June 1999. Results reported here are based on a database lock for the open-label extension as of June 2004. Maximum follow-up from TEMPO start to database lock was 6.5 years, but time in the study varied for subjects depending on their specific times of enrollment and discontinuation. All subjects enrolled in the extension provided written informed consent to participate, approved by the appropriate institutions.

Design and Study Treatment

The extension study was organized and sponsored by Teva Pharmaceutical Industries, Ltd. (Netanya, Israel) and Teva Neuroscience, Inc. (Horsham, PA). During the open-label extension, all subjects were initially treated with rasagiline 2 mg once daily. Following an amendment in mid-2000, the rasagiline dose was changed to 1 mg once daily because the 6-month TEMPO study found that the 2 mg/day dose did not provide significantly greater symptomatic efficacy than the 1 mg/day dose. In the open-label extension, subjects could be treated with all approved antiparkinson medications (except selegiline) as deemed appropriate by the investigator. Rasagiline was provided to the study sites by Teva Pharmaceutical Industries, and other PD medications were prescribed by treating investigators.

Assessments

In the extension study, subjects were assessed approximately every 3 months. During each visit, subjects were evaluated using UPDRS Mood, Mentation and Behavior (part I), Activities of Daily Living (ADL, part II), and motor (part III) subscales and were rated on the Hoehn and Yahr and Schwab-England scales. At each visit, the investigator determined if the subject had reached a level of functional disability sufficient to warrant the initiation of additional dopaminergic therapy if

it had not been added already, and PD medications other than rasagiline were adjusted as appropriate. The occurrence of fluctuations and dyskinesias was recorded using a separate questionnaire, which was distributed to investigators after the open-label study was already in progress. Because of this, data regarding motor fluctuations and dyskinesias are available for a total of 211 subjects only. Adverse event (AE) information was also collected at each visit.

Statistical Analysis

The primary efficacy measure was the adjusted mean change from TEMPO baseline to last observation in total UPDRS scores (parts I–III). UPDRS values were analyzed by half-year intervals using each subject's last observed value in each half-year period. This was a long-term study in which patients were not followed for a predefined amount of time, hence no imputation methods were used in order to take into account missing data due to loss of follow-up, and an intention to treat observed-cases (ITT-OC) cohort was analyzed. The mixed model repeated measures analysis (RMA) method was used to account for different observation periods for different patients. Comparisons were made between early- and delayed-start groups for UPDRS scores, percent change in UPDRS scores, and levodopa dose equivalents. Baseline total UPDRS score, treatment, time, treatment and time interaction, and treatment center were entered into the model as explanatory variables. RMA was also performed for UPDRS scores and percent change in UPDRS scores for those subjects who remained in the study at database lock ($n = 177$). Additional analyses included time from baseline to the start of additional dopaminergic therapy and percent of subjects on additional dopaminergic therapy. For each subject the total levodopa dose equivalent was calculated for the day prior to each UPDRS visit. Total levodopa dose equivalents were calculated as follows: (regular levodopa dose \times 1) + (levodopa controlled-release dose \times 0.75) + (pramipexole dose \times 67) + (ropinirole dose \times 16.67) + (pergolide dose \times 100) + (bromocriptine dose \times 10) + [(regular levodopa dose + [levodopa controlled-release dose \times 0.75]) \times 0.25 if taking tolcapone] + [(regular levodopa dose + [levodopa controlled-release dose \times 0.75]) \times 0.1 if taking entacapone].¹⁴

Tolerability and safety were assessed from the start of the TEMPO study. Outcomes included spontaneously reported AEs, investigator observation of any AEs, withdrawals due to AEs, and serious AEs.

RESULTS

Subjects

The original ITT efficacy population included 404 subjects from the TEMPO study. Of those, 266 were randomly assigned to initial (early) treatment with rasagiline 1 mg or 2 mg, and 138 were initially randomly assigned to placebo (delayed rasagiline start) (Fig. 1). Six delayed-start subjects withdrew from the study prior to the start of the active treatment phase of TEMPO and never received rasagiline. Table 1 summarizes baseline demographic and clinical characteristics of ITT subjects by original treatment assignment. The treatment groups were comparable with regard to age, sex, and PD characteristics. A total of 360 subjects completed TEMPO and were therefore eligible to enter the extension study; 306 subjects (85% of the 360 subjects who completed the double-blind portion of the trial) chose to participate in the open-label extension study.

Average (\pm SD) duration in the study for all subjects in the ITT-OC cohort was 3.6 ± 2.1 years and did not differ by group. Mean (\pm SD) time in the study was 3.5 ± 2.2 years in the early-start group and 3.6 ± 2.1 years in the delayed-start group; 177 subjects continued to receive rasagiline at the time of database lock (Fig. 1).

Efficacy Results

Change From TEMPO Baseline to Last Observation in Total UPDRS

For the entire observation period of 6.5 years, the adjusted mean difference in change from baseline total UPDRS was 2.5 units (SE 1.1) ($P = 0.021$) in favor of the early-start group versus the delayed-start rasagiline group. This corresponds to a mean relative difference in percent change from baseline between groups of 16% (SE 5.7; $P = 0.006$) (Fig. 2). Although the interaction between treatment and time was significant for both analyses ($P = 0.0146$ for change in UPDRS scores and $P = 0.0126$ for percent change in UPDRS scores), values for the early-start group were numerically better than the delayed-start group across all time points (Fig. 2 and data not shown) and this interaction reflects the variability observed in the differences between the early-start and delayed-start groups including a decrease in differences after 1 year as compared to 6 months and an increase in the differences after 4 years. Analysis by half-year intervals revealed significantly less worsening in percent change in total UPDRS scores in the early-start group at

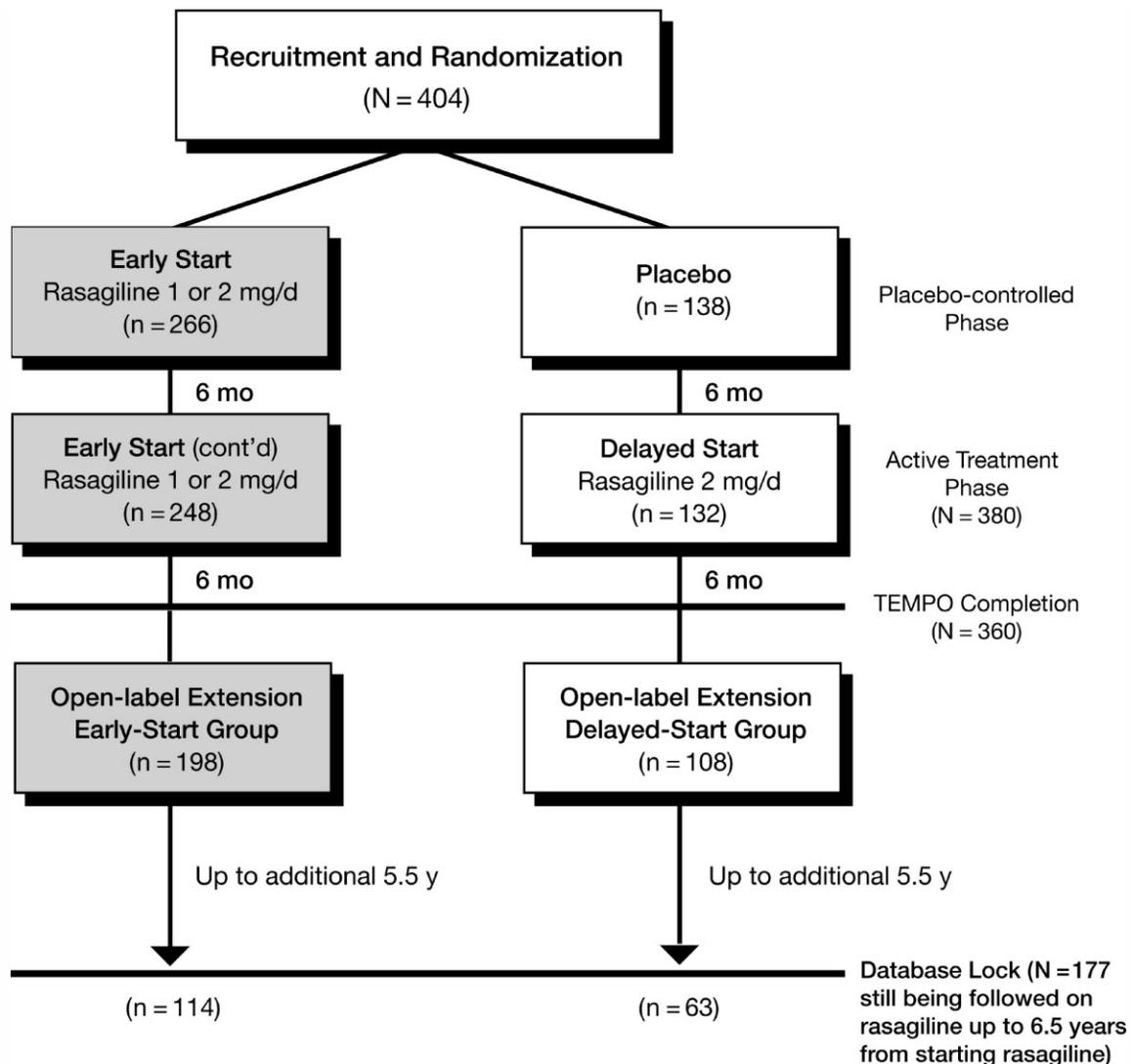


FIG. 1. Design and subject disposition for intent-to-treat population in the TEMPO study and its open-label extension. During the first 6 months of TEMPO, subjects were assigned to rasagiline 1 mg/day, 2 mg/day, or placebo. In the second 6 months, those previously given placebo were started on rasagiline 2 mg/day. At TEMPO completion, subjects who chose to enter the open-label extension were initially administered rasagiline 2 mg/day. Following a protocol amendment, all subjects were switched to rasagiline 1 mg/day between June and November 2000. This change was instituted after the TEMPO 6-month analysis showed no increase in efficacy at the 2-mg dose compared to the 1-mg dose. Subjects in the open-label study received rasagiline 2 mg/day for an average of 10.8 months.

0.5, 1.5, 2.0, 3.0, 4.5, 5.0, and 5.5 years ($P < 0.05$). Changes in motor- and ADL-UPDRS scores also favored the early-start group with mean differences in percent change from baseline between groups of 11.9% (SE 5.9; $P = 0.046$) and 39.1% (SE 17.7; $P = 0.028$), respectively.

Of the 177 subjects who remained in the study at database lock, 114 were from the early-start and 63 were from the delayed-start group, consistent with the original randomization ratio. Mean (SD) time on rassa-

giline was 5.6 ± 0.4 years for the early-start group and 5.5 ± 0.4 years for the delayed-start group. Baseline characteristics of subjects remaining in the study at database lock compared to the original ITT population included slightly longer times from PD diagnosis and somewhat lower mean total UPDRS scores and Hoehn and Yahr stages (Table 1). For the 177 ongoing subjects, the adjusted mean difference in total UPDRS scores was 2.42 units (SE ± 1.04 ; $P = 0.0218$) in favor of the early-start group, corresponding to a mean relative

TABLE 1. Baseline demographic, clinical, and treatment characteristics

Characteristic	Early-start group, ITT-OC (N = 266)	Early-start group, remaining at database lock (N = 114)	Delayed-start group, ITT-OC (N = 138)	Delayed-start group, remaining at database lock (N = 63)
Mean age (±SD), yr	61.0 ± 10.8	61.0 ± 10.1	60.5 ± 10.8	59.6 ± 10.8
Sex, % male	61.7	64.9	67.4	66.7
Mean PD duration (±SD), yr	1.0 ± 1.3	1.2 ± 1.5	0.9 ± 1.1	1.1 ± 1.3
Mean total UPDRS score (±SD)	25.3 ± 10.4	24.7 ± 10.8	24.5 ± 11.6	21.0 ± 8.9
Mean Hoehn & Yahr stage (±SD)	1.9 ± 0.5	1.8 ± 0.4	1.9 ± 0.5	1.7 ± 0.1
Mean years in study (range)	3.5 (0.0–6.5)	5.6 (4.6–6.5)	3.6 (0.1–6.4)	5.5 (4.7–6.4)
Median years from start to addition of dopamine agonist or levodopa	1.5	2.1	1.8	2.5
% of subjects who received dopamine agonist or levodopa ^a	65.8	83.3	70.3	85.7
Median years from start to addition of levodopa	4.1	4.3	4.2	5.1
% of subjects who received levodopa ^a	46.2	69.3	44.2	55.6

ITT-OC indicates intent-to-treat observed-cases population.

Demographics and treatment characteristics of early-start and delayed-start groups were compared by *t*-test for continuous variables and Chi-square test for categorical variables. Between-group differences were not significant.

^aAt any time from baseline to study end.

difference in percent change from baseline of 17% (SE ± 5.4; *P* = 0.002).

Additional Dopaminergic Medication

Median time from TEMPO baseline to additional dopaminergic treatment was similar for the early- and

delayed-start ITT-OC groups (1.5 years and 1.8 years, respectively; NS) (Table 1). Likewise, the percent of subjects receiving levodopa or additional dopaminergic treatment was comparable for the early- and delayed-start groups in both the ITT-OC and ongoing patient cohorts. Similarly, levodopa dosage equivalents did not differ significantly at any half-year interval for the

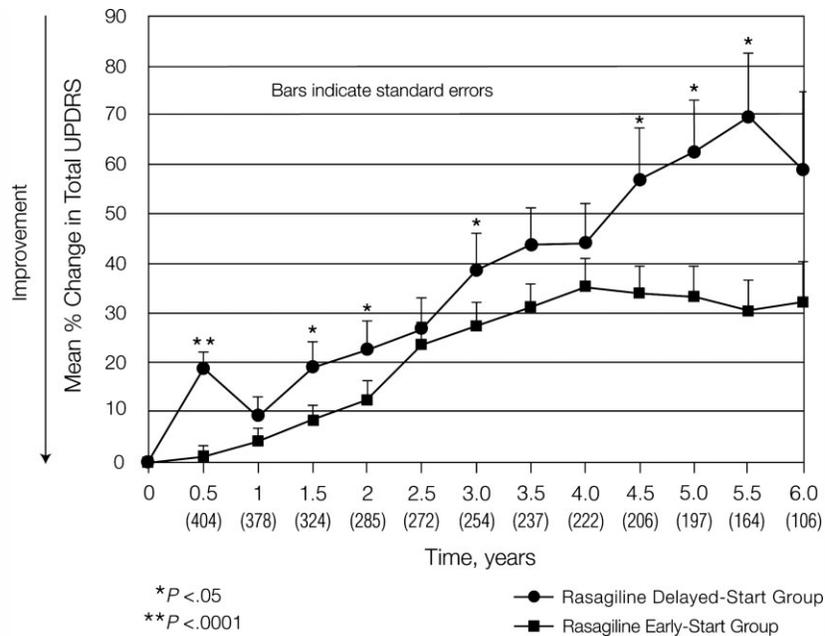


FIG. 2. Mean percent change from TEMPO baseline in total UPDRS scores: early-start versus delayed-start with rasagiline (N = 404). Overall difference between early-start and delayed-start groups is 16% (RMA; *P* = 0.006). Numbers in parentheses () represent numbers of subjects remaining on rasagiline at each time point. The analysis of UPDRS scores was performed at each time point according to available patient visits, and not necessarily synchronized with TEMPO placebo-controlled and active-treatment phases shown in Figure 1. Bars indicate standard errors. Data from year 6.5 are combined with data from year 6.

early- or delayed-start groups regardless of whether the ITT-OC population or remaining subjects at database lock were considered (Table 2).

Motor Complications

For the 211 subjects for whom fluctuation and dyskinesia information was collected, median time (derived from Kaplan-Meier estimates) to fluctuations was 6.1 years in the early-start group (n = 75) and 6.0 years in the delayed-start group (n = 136). Median time to develop dyskinesias was not reached, but time for 25% of subjects to experience dyskinesia was comparable in the two groups, 5.2 versus 5.9 years. Earliest time to either fluctuations or dyskinesia was 5.5 years in both the early-start and delayed-start groups. None of these differences were significant using the log-rank test. All patients on rasagiline who reported dyskinesia were being treated with levodopa, and most (75.5%) were also taking a dopamine agonist. Similarly, all patients with fluctuations were receiving levodopa (16.9%), a dopamine agonist (15.7%), or both (67.4%).

Tolerability and Safety

Information regarding the most common AEs observed in the entire study (those occurring most frequently on a basis of 1000 patient-years) is provided in Table 3. Most subjects in each group reported at least one AE over the course of this long-term follow-up study (260/266, 97.7% early-start; 131/132, 99.2% delayed-start), and similar percentages of subjects in each group experienced AEs leading to termination (28/266, 10.5% early-start; 15/132, 11.4% delayed-start). The most common AEs overall were infection, accidental injury, dizziness, sleep disorder, and nausea.

DISCUSSION

In this delayed-start, open-label extension study, earlier initiation of rasagiline was associated with slower long-term progression of clinical signs and symptoms of PD. In the original double-blind, delayed-start study, subjects treated with rasagiline 1 mg/day or 2 mg/day for 1 year had significantly less worsening when compared with subjects treated with placebo for 6 months followed by rasagiline 2 mg/day for 6 months. During the extension phase of the study reported here, subjects continued to receive rasagiline, and other PD medications (except selegiline) could be added and adjusted as necessary. For the entire follow-up period of 6.5 years, the mean difference in change from baseline in

TABLE 2. Antiparkinson medication added over time, in levodopa dosage equivalents, and differences in % change in UPDRS scores

Year	Levodopa dosage equivalents (Mean ± SE)											
	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6
Early start	NA	145 ± 415	283 ± 526	359 ± 539	450 ± 647	536 ± 688	639 ± 779	822 ± 936	1038 ± 1263	1204 ± 1301	1293 ± 1535	1143 ± 1189
Delayed start	NA	131 ± 318	184 ± 426	279 ± 503	400 ± 608	482 ± 707	560 ± 749	706 ± 878	796 ± 901	899 ± 1098	1069 ± 1296	1447 ± 1933
Difference in mean % change from TEMPO baseline in total UPDRS scores	17.72	5.08	10.57	10.02	3.25	11.31	12.3	8.71	23.0	29.32	39.34	26.73

During the open-label extension, subjects remained on rasagiline and investigators added dopamine agonists or levodopa when they felt it was required. This table shows the amount of adjunctive medication taken at 6-month intervals during the open-label extension, converted to levodopa equivalents according to the formula given in the Methods section. Statistical analysis revealed no significant differences in mean levodopa equivalents between the early-start and delayed-start groups at any time point.

TABLE 3. Most common adverse events

Adverse event	Early start (<i>n</i> = 266,* patient-yr = 939.4)		Delayed start (<i>n</i> = 132,* patient-yr = 500.1)	
	No. (%) subjects with AE**	No./1000 patient-yr	No. (%) subjects with AE**	No./1000 patient-yr
All	260 (97.7)	276.8	131 (99.2)	261.9
Serious	86 (32.3)	91.5	44 (33.3)	88.0
Leading to termination	28 (10.5)	29.8	15 (11.4)	30.0
All reported incidences of the following:				
Infection	94 (35.3)	100.1	52 (39.4)	104.0
Accidental injury	86 (32.3)	91.5	43 (32.6)	86.0
Dizziness	56 (21.1)	59.6	40 (30.3)	80.0
Sleep disorder	52 (19.5)	55.4	34 (25.8)	68.0
Nausea	69 (25.9)	73.5	33 (25.0)	66.0
Back pain	55 (20.7)	58.5	33 (25.0)	66.0
Pain	57 (21.4)	60.7	32 (24.2)	64.0
Peripheral edema	53 (19.9)	56.4	29 (22.0)	58.0
Constipation	51 (19.2)	54.3	27 (20.5)	54.0
Headache	61 (22.9)	64.9	25 (18.9)	50.0
Arthralgia	70 (26.3)	74.5	23 (17.4)	46.0
Somnolence	54 (20.3)	57.5	21 (15.9)	42.0

Adverse events occurring most frequently on a basis of 1,000 patient-yr from TEMPO start. AE indicates adverse event.

*Randomization was in a 2 to 1 ratio.

**Duration of time on rasagiline varied from 6 months to 6.5 yr. To facilitate comparison between early-start and delayed-start groups, AEs are presented per unit of time in shaded columns.

total UPDRS scores between early- and delayed-start subjects was 2.5 units ($P = 0.021$), corresponding to a mean relative difference of 16% ($P = 0.006$). Similarly, for subjects who continued in the study up to database lock, the adjusted mean difference in change in total UPDRS scores was 2.4 units, corresponding to a mean relative difference of 17% ($P = 0.002$) in favor of the early-start rasagiline group. This suggests that early treatment with rasagiline may offer clinical benefits compared to a delay of treatment for 6 months, and these benefits may be enduring and apparent even as patients are treated with other PD medications.

These findings must be interpreted cautiously given the open-label design of the extension study and the fact that the repeated measures analyses were performed on an intention to treat-observed cases (ITT-OC) cohort. Although the magnitude of difference between early and delayed-start groups varied over time, the early-start group was always numerically better as assessed by UPDRS scores, and the overall difference between groups indicates that the early-start group, on average, performed better than the delayed-start group. Significant differences were noted at over half of the individual time points and the magnitude of difference was greatest with longer follow-up (4.5–5.5 years).

Over the 6.5 years of observation, about half of the subjects withdrew from the study. Baseline characteris-

tics of subjects remaining in the study at database lock included slightly longer times from PD diagnosis, and somewhat lower mean total UPDRS scores and Hoehn and Yahr stages, suggesting these subjects had slower progression of disease than those who withdrew from the study. Also, the mechanism underlying the observed slower rate of clinical progression in the early-start group remains to be determined. Although the early-start group was receiving numerically more levodopa dose equivalents (except at year 6), no significant difference was seen in the levodopa dose equivalents between the two groups. Nonetheless, we cannot exclude the possibility that a nonsignificant difference in levodopa dose equivalents could lead to a significant difference in clinical benefit. Of note, we did not observe a higher incidence of motor complications or dopaminergic side effects in the early-start group that, if present, might have signaled a clinically meaningful difference in levodopa dose equivalents.

Another possibility is that the early introduction of any symptomatic PD medication will lead to a better clinical outcome¹⁵ compared to delayed administration, possibly due to effects on endogenous compensatory mechanisms. This possibility will have to be evaluated as delayed-start studies are performed with other PD medications. In a rotigotine open-label study that mimicked a delayed-start design, no differences in UPDRS scores were identified once subjects in the delayed-start group received rotigotine,¹⁶ arguing against a general-

ized phenomenon. In addition, the DATATOP selegiline study can also be viewed as mimicking a delayed-start design, and once selegiline was administered to the original placebo group, there were no differences in UPDRS scores.¹⁷

The long-term benefit observed with early initiation of rasagiline could be due to a neuroprotective effect. In multiple cell culture and animal models, rasagiline has a proven neuroprotective effect.^{10,11,18} Rasagiline reduces neuronal loss in animal models of *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration,⁵ oxidative stress,⁶ hypoxic injury,⁷ cerebral trauma,⁸ and amyotrophic lateral sclerosis (ALS).⁹ The neuroprotective activity of rasagiline appears to be independent of MAO-inhibition.¹⁰ Its propargylamine moiety protects mitochondrial viability and the mitochondrial permeability transition pore by activating Bcl-2 and protein kinase C, and downregulating proapoptotic FAS and Bax.^{10,11} Rasagiline also increases nerve growth factor, glial cell-derived neurotrophic factor, and brain-derived neurotrophic factor.¹² If rasagiline provides neuroprotection in PD patients, early-start subjects might have experienced this benefit from the beginning of the TEMPO study, whereas delayed-start subjects would not have been exposed to it for the first 6 months. This could potentially lead to an enduring benefit in terms of neuronal viability and provide a long-term clinical advantage. If this is the case, both early diagnosis and treatment may be important.

The delayed-start study design was initially devised as a methodology to evaluate potential neuroprotective effects of medications that might have confounding symptomatic effects,¹⁹ but it is not without limitations.²⁰ There are concerns that the rate of progression of PD is not linear, that all symptomatic medications may produce positive results in delayed-start trials, that there may be poor generalizability due to selection of patients with slower disease progression, and that changes in UPDRS scores may not be clinically significant. Further studies are warranted to confirm the findings of the TEMPO delayed-start rasagiline study and this long-term extension. In fact, a large and rigorous delayed-start study of rasagiline in 1176 early PD patients (ADAGIO: Attenuation of Disease progression with Azilect Given Once-daily) is currently underway.²¹ Further investigations are also required to understand the mechanisms that may underlie positive results from delayed-start studies. No reliable quantitative biomarkers are currently available for PD, and clinical trials cannot unequivocally prove neuroprotection.²² Rasagiline might be considered for a long-term,

double-blind trial in which subjects are randomly assigned to placebo or rasagiline and can receive all other available types of PD medications as appropriate, to assess the long-term benefit of rasagiline on multiple spheres of the disease, regardless of the underlying mechanism.²³

Rasagiline appeared to be well-tolerated in this long-term study, with 10% to 12% of subjects withdrawing due to adverse events over the 6.5 year observation period. In addition, there were no reports of hypertensive crisis or serotonin syndrome. Rasagiline was administered once daily and appears to be suitable for long-term use. Current information from TEMPO and this extension suggests that early treatment with rasagiline offers greater long-term benefits to PD patients compared to delayed treatment, and these benefits are observed even as patients receive conventional symptomatic therapy.

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Contributor Roles: Robert A. Hauser: wrote first draft, revised draft based on input from all authors, analysis and interpretation of data, participation in analysis design, acquisition of data. Mark F. Lew, Howard I. Hurtig, William G. Ondo, Joanne Wojcieszek: data acquisition, review and interpretation of data, critical revision of draft. Cheryl J. Fitzer-Attas: organization of study, statistical expertise, analysis and interpretation of data, critical revision of draft. Dr. Hauser drafted the manuscript and revised it based on input from all authors. No compensation was provided to Drs. Hauser, Lew, Hurtig, Ondo, or Wojcieszek, for their work on this manuscript. The statistical analyses were conducted by Sivan Weiss, Ziv Shachar, Sergey Goichman, and Galia Shifroni of Teva Pharmaceutical Industries, Ltd.

APPENDIX

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