

A Controlled, Randomized, Delayed-Start Study of Rasagiline in Early Parkinson Disease

Parkinson Study Group

Background: Treatment with rasagiline mesylate, an irreversible monoamine oxidase type B inhibitor, improves symptoms of early Parkinson disease (PD). Pre-clinical studies suggest that this compound may also modify the progression of PD.

Objective: To compare the effects of early and later initiation of rasagiline on progression of disability in patients with PD.

Design: Double-blind, parallel-group, randomized, delayed-start clinical trial.

Settings and Patients: Four hundred four subjects with early PD, not requiring dopaminergic therapy, enrolled at 32 sites in the United States and Canada.

Interventions: Subjects were randomized to receive rasagiline, 1 or 2 mg/d, for 1 year or placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months.

Main Outcome Measure: Change in total Unified Parkinson's Disease Rating Scale score from baseline to 12 months.

Results: Three hundred seventy-one subjects were included in the 1-year efficacy analysis. Subjects treated with rasagiline, 2 mg/d, for 1 year had a 2.29-unit smaller increase in mean adjusted total Unified Parkinson's Disease Rating Scale score compared with subjects treated with placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months ($P = .01$). The mean adjusted difference between the placebo/rasagiline, 2 mg/d, group and those receiving rasagiline, 1 mg/d, for 1 year was -1.82 unit on the Unified Parkinson's Disease Rating Scale score ($P = .05$).

Conclusion: Subjects treated with rasagiline, 2 and 1 mg/d, for 12 months showed less functional decline than subjects whose treatment was delayed for 6 months.

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RASAGILINE (*N*-PROPARGYL-1 [R]-aminoindan) mesylate (TVP-1012) is a selective irreversible inhibitor of monoamine oxidase type B.¹ It is highly effective in antagonizing *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced nigral damage in animal models of Parkinson disease (PD),² and prevents nigral cell death in vitro by enhancing the expression of antiapoptotic and neurotrophic factors.^{3,4} In a 10-week randomized, controlled, pilot study⁵ of subjects with early untreated PD, dosages of rasagiline up to 4 mg/d were well tolerated.

In the present study, we randomized 404 subjects with early otherwise untreated PD to receive either rasagiline, 1 or 2 mg/d, or matching placebo. We have previously reported the initial 6-month placebo-controlled phase of this trial. This initial phase showed that subjects receiving once-daily rasagiline had better symp-

tom control than those receiving placebo.⁶ In this second phase, subjects randomized to 1 or 2 mg/d of rasagiline continued to receive that dosage, while subjects previously taking placebo received rasagiline, 2 mg/d. The 1-year data have been analyzed as a randomized, delayed-start, clinical trial.⁷ This analysis assesses whether earlier initiation of rasagiline resulted in better functional status at 1 year when all participants were receiving active treatment and the symptomatic effect of rasagiline was presumably balanced among groups.

METHODS

SUBJECTS

Subjects were enrolled at participating centers in the United States and Canada between November 1997 and June 1999. Eligible subjects were older than 35 years, had idiopathic PD confirmed by the presence of at least 2 of

A list of the Parkinson Study Group TEMPO investigators was published previously (*Arch Neurol.* 2002;59:1937-1943).

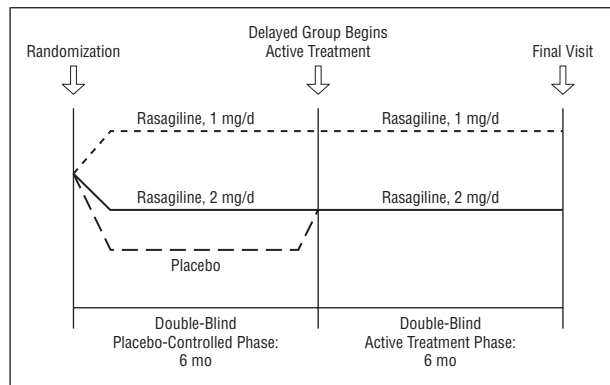


Figure 1. The randomized delayed-start trial design. In one arm of the trial, initiation of active treatment was delayed for 6 months. All subjects were receiving active treatment at the end of the trial. Rasagiline was administered as rasagiline mesylate.

the cardinal signs (resting tremor, bradykinesia, and rigidity), and had disease severity not greater than Hoehn and Yahr⁸ stage III. At enrollment, subjects could be treated with anticholinergic medications, but other antiparkinsonian medications were not permitted. Likewise, use of antidepressants other than amitriptyline hydrochloride, paroxetine, sertraline hydrochloride, fluvoxamine maleate, or trazodone hydrochloride and use of sympathomimetic agents were not permitted.

DESIGN AND STUDY TREATMENT

The study used a randomized delayed-start design (**Figure 1**). It was organized by the Parkinson Study Group, and sponsored by Teva Pharmaceutical Industries, Ltd (Netanya, Israel) and Teva Neuroscience, Inc (North Wales, Pa). After informed consent was obtained, subjects were randomized to 1 of 3 treatment groups: (1) rasagiline, 1 mg/d, for 1 year; (2) rasagiline, 2 mg/d, for 1 year; or (3) matching placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months. The methods of the initial 6-month placebo-controlled phase have been described previously.⁶ Blinding was maintained in all phases. Subjects entered the active treatment phase at 6 months, unless the investigator determined the subject required additional dopaminergic therapy earlier, which led to sooner entry into the active treatment phase. Subjects who continued to need additional therapy after entering the active treatment phase were treated with either a combination of carbidopa and levodopa or a dopamine agonist.

ASSESSMENTS

Subjects were examined at baseline and at 4, 8, 14, 20, 26, 32, 42, and 52 weeks after randomization. At each examination, the investigator rated the subjects with the Unified Parkinson's Disease Rating Scale (UPDRS),⁹ including mental, activities of daily living, and motor subscales. Subjects were also rated on the Hoehn and Yahr⁸ and Schwab and England¹⁰ activities of daily living scales. At each follow-up examination, the investigator determined if the subject had reached a level of functional disability sufficient to warrant the initiation of additional dopaminergic therapy. Subjects were assessed for adverse experiences and underwent a battery of laboratory tests at each visit.

STATISTICAL ANALYSIS

The primary statistical analyses were performed according to the intention-to-treat principle, including all subjects who entered the active treatment phase of the trial. If a subject needed dopaminergic therapy or withdrew after at least 1 efficacy as-

essment in the active treatment phase (n = 112), the last available observation was carried forward for the week 52 visit. Subjects who withdrew before having at least 1 efficacy assessment in the active treatment phase were not included in the efficacy analysis.

The primary measure of efficacy was the change in total UPDRS score from baseline to the week 52 visit. Secondary measures of efficacy included the proportion of responders, defined as subjects whose UPDRS score decreased by fewer than 4 units during the study, roughly 50% of the expected change without treatment over 1 year. Other secondary efficacy measures included changes in the mental, activities of daily living, and motor subscales of the UPDRS. The time from baseline to the start of dopaminergic therapy (either carbidopa-levodopa or a dopamine agonist) was also analyzed. Safety was measured by the frequency and severity of adverse events.

An analysis of covariance was used to compare changes from baseline to the final visit for each 1-year treatment group vs the delayed-treatment group. Baseline values and treating center were included as covariates. The treatment × center interaction term was included in the model if it was statistically significant at $P < .05$. For each variable analyzed, effect size was defined as the difference between adjusted means for each 1-year rasagiline group vs the delayed rasagiline group. Nominal P values (not adjusted for multiple comparisons) are reported for all analyses.

To determine the impact of early withdrawals, the primary efficacy analysis was repeated including only subjects who were treated for the entire 52 weeks of the study. Analyses were also repeated for all subjects, including those who participated in the double-blind phase but did not reach the active-treatment phase. To assess the effect of differential duration of follow-up in the study, the proportion of subjects who entered the active treatment phase before 26 weeks, the proportion completing all 52 weeks of the trial, and the total number of days spent in the trial were compared by treatment group.

Analyses of safety measures were descriptive. The frequencies of individual adverse events and abnormal laboratory test results, vital signs, and electrocardiographic results were analyzed, with imbalances among treatment groups flagged at a nominal 5% level.

RESULTS

PROGRESS OF SUBJECTS THROUGH THE STUDY

Of the 404 subjects who were randomized, 380 entered the active treatment phase. Nine patients who received additional dopaminergic therapy or withdrew immediately following entrance to the active treatment phase (before the first efficacy assessment) were not included in the efficacy analysis. The other 371 patients (91.8%) formed the intention-to-treat cohort for the primary analysis (efficacy cohort) (**Figure 2**). The 33 subjects who withdrew or began dopaminergic therapy immediately were older (64.8 vs 60.5 years; $P = .04$) and had higher total UPDRS scores at baseline (31.5 vs 24.5; $P < .001$).

There were no significant differences in baseline characteristics among treatment groups for the 371 subjects who participated in the active treatment phase (**Table 1**). Of these subjects, 325 entered after completing 26 weeks in the placebo-controlled phase, without needing additional therapy. Forty-six subjects participated in the active treatment phase without first completing the entire 26 weeks in the placebo-controlled phase because they

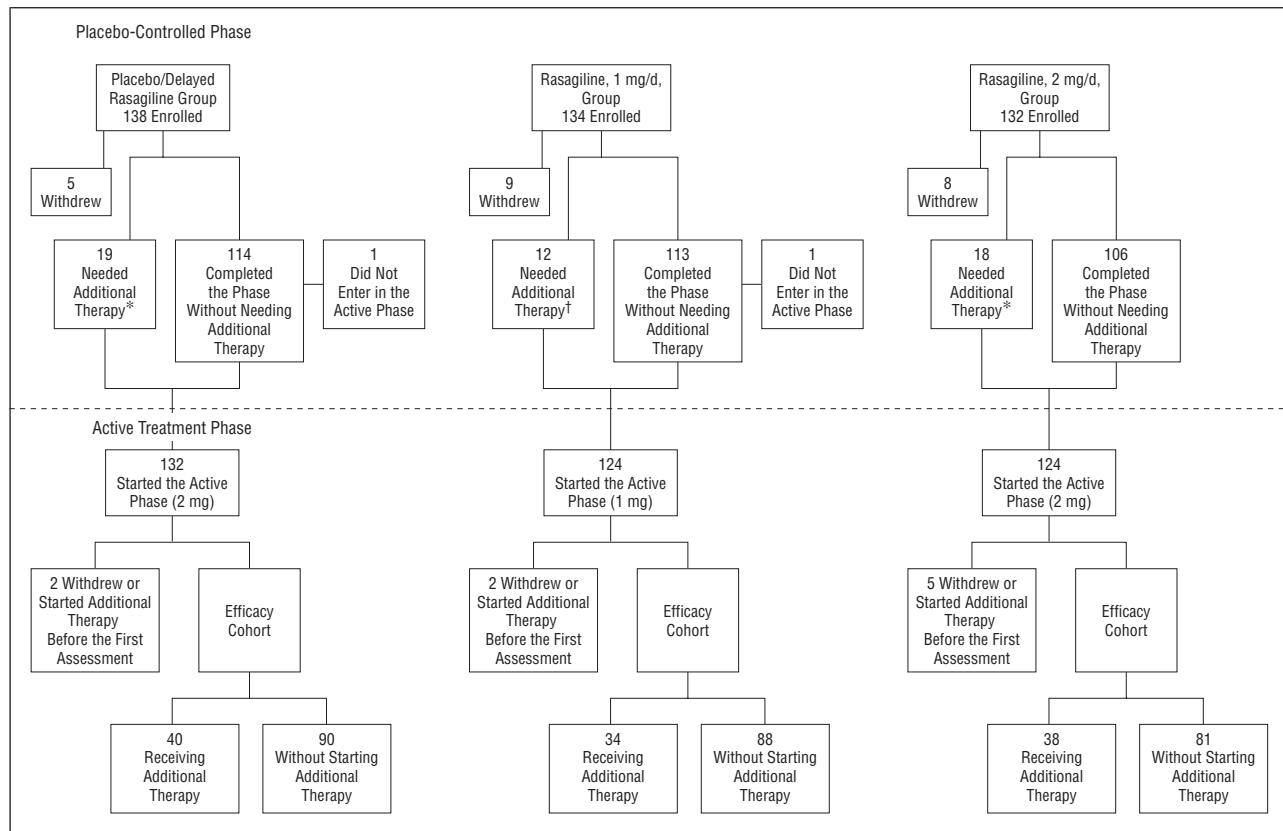


Figure 2. Subjects entering the study. The flow diagram shows the progression of subjects from randomization to completion of the study. Rasagiline was administered as rasagiline mesylate. The asterisk indicates that 4 of these subjects completed the active phase without starting additional actual treatment; and the dagger, 2 of these subjects completed the active phase without starting additional actual treatment.

were determined to need additional therapy during the first phase. A total of 259 subjects (69.8% of the efficacy cohort) completed the active phase without starting additional therapy. There were no differences by treatment group in the number of subjects reaching the active treatment phase or in the mean number of days subjects spent in the trial.

ANALYSIS OF EFFICACY MEASURES

The 52-week total UPDRS (last observation carried forward) mean (\pm SD) scores for the 371 participating subjects were 27.45 (14.18), 27.10 (11.90), and 28.02 (14.17) for the 1-mg, 2-mg, and delayed 2-mg groups, respectively. The mean (SD) changes in total UPDRS from baseline were 3.01 (8.26), 1.97 (7.49), and 4.17 (8.83), respectively (**Figure 3A**).

The effect of treatment (calculated by the difference between adjusted means of the analysis of covariance model) on total UPDRS score comparing rasagiline, 1 mg/d, for 1 year with delayed rasagiline, 2 mg/d, was -1.82 units (95% confidence interval, -3.64 to 0.01 units) ($P = .05$); and the effect size comparing rasagiline, 2 mg/d, for 1 year with delayed rasagiline, 2 mg/d, was -2.29 units (95% confidence interval, -4.11 to -0.48 units) ($P = .01$) (**Table 2**). Comparisons of the total UPDRS score between treatment groups for the entire cohort of 404 subjects were similar to those for the active treatment cohort. Analyses of the 249 subjects who were treated for the full 52 weeks without start-

Table 1. Baseline Characteristics of the Study Cohort by Treatment Group*

Characteristic	Treatment Group			P Value†
	Delayed Rasagiline, 2 mg/d (n = 130)	Rasagiline, 1 mg/d (n = 122)	Rasagiline, 2 mg/d (n = 119)	
Age, y	60.4 \pm 10.9	60.8 \pm 10.1	60.2 \pm 11.4	.96
Disease duration, y	0.90 \pm 1.08	0.92 \pm 1.28	1.13 \pm 1.31	.32
Male sex‡	89 (68.5)	82 (67.2)	68 (57.1)	.13
UPDRS score				
Total	23.9 \pm 10.9	24.4 \pm 11.5	25.1 \pm 9.1	.27
Motor	17.0 \pm 8.3	17.6 \pm 9.1	17.5 \pm 7.2	.72
ADL	6.01 \pm 3.32	5.95 \pm 3.41	6.53 \pm 3.22	.16
Mental	0.82 \pm 1.09	0.93 \pm 1.09	1.11 \pm 1.23	.13
Schwab and England ¹⁰ scale score	91.4 \pm 6.1	92.2 \pm 5.7	90.7 \pm 5.6	.16
Hoehn and Yahr ⁸ scale score	1.84 \pm 0.49	1.84 \pm 0.48	1.85 \pm 0.47	.99

Abbreviations: ADL, activities of daily living; UPDRS, Unified Parkinson's Disease Rating Scale.

*Data are given as mean \pm SD unless otherwise indicated. Rasagiline was administered as rasagiline mesylate.

†The Kruskal-Wallis test or the χ^2 test was used, as appropriate.

‡Data are given as number (percentage) of subjects in each group.

ing additional therapy also showed similar results; however, the comparisons for this smaller group were not statistically significant (Figure 3B).

Table 2. Change From Baseline in Efficacy Variables Between the 371 Subjects Receiving 6 Months and 1 Year of Treatment*

Variable	Rasagiline, 1 mg/d vs Delayed Rasagiline, 2 mg/d	Rasagiline, 2 mg/d, vs Delayed Rasagiline, 2 mg/d
UPDRS		
Total†	-1.82 (-3.64 to 0.01)‡	-2.29 (-4.11 to -0.48)§
Motor†	-1.06 (-2.47 to 0.34)	-0.99 (-2.39 to 0.41)
ADL	-0.48 (-1.15 to 0.19)	-0.96 (-1.64 to -0.29)
Mental†	0.16 (-0.09 to 0.42)	-0.07 (-0.33 to 0.19)
Hoehn and Yahr ⁸ scale score	0.08 (-0.01 to 0.17)	0.04 (-0.05 to 0.13)
Schwab and England ¹⁰ scale score	-0.21 (-1.47 to 1.04)	-0.15 (-1.41 to 1.11)

Abbreviations: See Table 1.

*Data are given as effect size (95% confidence interval). Rasagiline was administered as rasagiline mesylate.

†The model used to determine effect size includes a treatment × center interaction.

‡ $P = .05$.

§ $P = .01$.

|| $P = .005$.

In the efficacy cohort, 76 (63.8%) of the subjects receiving rasagiline, 2 mg/d, for 1 year, 64 (52.5%) of those receiving rasagiline, 1 mg/d, for 1 year, and 68 (52.3%) of those in the delayed rasagiline, 2-mg/d, group were considered responders. The comparison of responders between the group receiving 2-mg/d rasagiline for 1 year and the delayed 2-mg/d rasagiline group was significant ($P = .04$). The comparison between the 1-mg/d rasagiline group and the delayed 2-mg/d rasagiline group was not significant ($P = .93$).

The comparison of activities of daily living scores of subjects receiving rasagiline, 2 mg/d, for 1 year with those receiving delayed rasagiline, 2 mg/d, for 6 months significantly favored longer treatment ($P = .005$) (Table 2). Comparisons of other subscales (mental and motor) were not significant. There were no differences between groups in the time to start additional therapy during 1 year of follow-up.

ANALYSIS OF SAFETY AND TOLERABILITY MEASURES

Details of adverse events occurring in the first 6 months have been reported previously.⁶ The most commonly observed adverse experiences during the active treatment phase were as follows: infection (10.8%), headache (5.4%), unintentional injury (4.9%), and dizziness (4.6%) (Table 3). There was no case in which an individual adverse event was significantly more frequent in subjects originally assigned to rasagiline than in those originally assigned to placebo. Serious adverse experiences included 5 newly diagnosed neoplasms and 17 hospitalizations. The newly diagnosed neoplasms included 1 case of colon cancer, 2 cases of squamous cell carcinoma of the skin, 1 case of basal cell carcinoma, and 1 case of melanoma. Hospitalizations occurred for a range of disorders, including vascular disease ($n = 6$), gastrointestinal symptoms ($n = 4$), un-

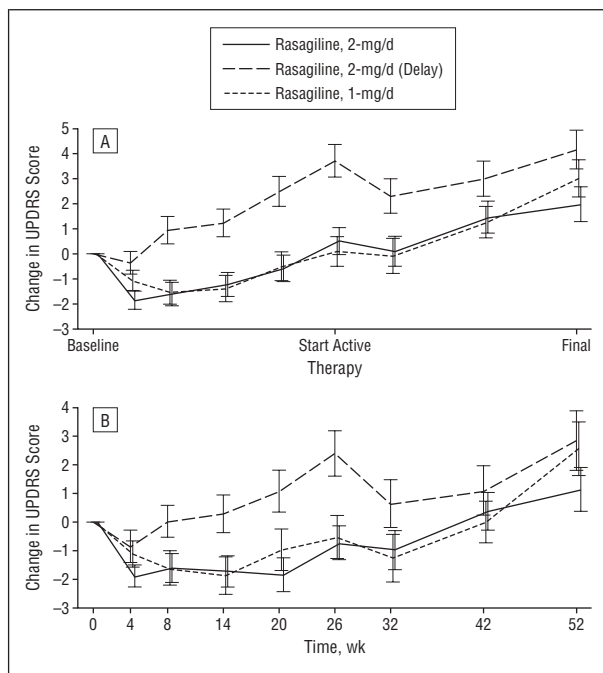


Figure 3. Mean (± 1 SE) change in the Unified Parkinson's Disease Rating Scale (UPDRS) score for each group. A, Total unadjusted UPDRS score by visit for each treatment group for the 371 subjects included in the efficacy cohort. For the efficacy cohort, the last observation was carried forward for subjects with missing values for a given visit. B, Unadjusted UPDRS score by visit for each treatment group for the 249 subjects who completed 52 weeks of treatment without starting additional therapy. Error bars indicate ± 1 SE.

intentional injuries ($n = 3$), and 1 case each of cellulitis, syncope, bronchitis, and vaginal prolapse.

COMMENT

This double-blind, randomized delayed-start, clinical trial showed that subjects treated with rasagiline at dosages of 1 and 2 mg/d for 1 year had less progression in total UPDRS scores than subjects for whom rasagiline treatment was delayed for 6 months. For subjects who reached the point of receiving active treatment, the effect of 1 year of rasagiline treatment was statistically significant compared with delaying rasagiline treatment by 6 months, and was detected over a relatively short period of observation.

The randomized delayed-start design used in this study was intended to separate an immediate symptomatic effect from an effect on disease progression.⁷ In this design, some subjects begin treatment at the start of the trial and others begin after a delay period. Because all subjects were receiving rasagiline in the second phase of the study, the symptomatic effects of the drug were presumably balanced at the last examination. Thus, the differences in performance observed at the final visit cannot be fully explained by the symptomatic effects of rasagiline.

One potential explanation of our results is that rasagiline slows the progression of disability of PD. Several mechanisms for this disease-modifying effect are possible. Rasagiline has been shown to protect neurons against hypoxic injury,¹¹ oxidative stress,¹² cerebral trauma,¹³ and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity in animal models,² and to exert

Table 3. Subjects Experiencing Adverse Events by Study Phase and Treatment Group*

Adverse Event	Treatment Group					
	Delayed Rasagiline, 2 mg/d (n = 130)		Rasagiline, 1 mg/d (n = 122)		Rasagiline, 2 mg/d (n = 119)	
	Placebo- Controlled Phase	Active Treatment Phase	Placebo- Controlled Phase	Active Treatment Phase	Placebo- Controlled Phase	Active Treatment Phase
Any event						
Any intensity	102 (78.5)	71 (54.6)	97 (79.5)	81 (66.4)	100 (84.0)	72 (60.5)
Moderate or severe intensity	57 (43.8)	35 (26.9)	50 (41.0)	39 (32.0)	53 (44.5)	44 (37.0)
Infection	20 (15.4)	15 (11.5)	19 (15.6)	16 (13.1)	19 (16.0)	9 (7.6)
Headache	11 (8.5)	5 (3.8)	18 (14.8)	6 (4.9)	16 (13.4)	9 (7.6)
Dizziness	14 (10.8)	4 (3.1)	9 (7.4)	4 (3.3)	9 (7.6)	9 (7.6)
Unintentional injury	13 (10.0)	7 (5.4)	9 (7.4)	4 (3.3)	9 (7.6)	7 (5.9)
Arthralgia	5 (3.8)	1 (0.8)	5 (4.1)	3 (2.5)	14 (11.8)†	5 (4.2)
Asthenia	13 (10.0)	3 (2.3)	6 (4.9)	3 (2.5)	5 (4.2)	2 (1.7)
Nausea	8 (6.2)	3 (2.3)	7 (5.7)	4 (3.3)	8 (6.7)	6 (5.0)
Back pain	6 (4.6)	4 (3.1)	7 (5.7)	8 (6.6)	8 (6.7)	3 (2.5)
Any serious adverse event	3 (2.3)	8 (6.2)‡	4 (3.3)	4 (3.3)	7 (5.9)	9 (7.6)

*Data are given as number (percentage) of subjects in each group. Rasagiline was administered as rasagiline mesylate.

†Statistically significant at the nominal $P = .05$ level (not corrected for multiple comparisons).

‡One subject in this group experienced 2 immediately reportable adverse events.

an antiapoptotic effect in cell cultures by enhancing the expression of the antiapoptotic protein Bcl-2.^{12,14} The major metabolite of rasagiline, aminoindan, also shows dose-dependent inhibition of apoptosis in cell culture models.¹⁵ It is also possible that rasagiline promotes better function of surviving dopaminergic neurons, improves the connectivity of these neurons, or acts through another unidentified mechanism.

Previous studies of selective monoamine oxidase type B inhibitors have been difficult to interpret because of the problem of distinguishing symptomatic effects from an effect on disease progression. One way that prior studies have addressed this problem has been to use a washout period at the end of the study. In the DATATOP (Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism) trial¹⁶ and in a placebo-controlled trial of lazabemide,¹⁷ there were small differences in total UPDRS scores compared with placebo after washout periods. However, washout periods to control for symptomatic effects have inherent problems. First, treatments may have durable pharmacodynamic effects, and the extent of these effects may be difficult to estimate. Second, subjects with more severe symptoms often cannot tolerate discontinuing a symptomatic medication and, thus, subjects with less severe manifestations of disease may be preferentially retained in the study.

A randomized delayed-start trial avoids these problems, but does have its own limitations. One of these is that symptomatic effects could be greater if therapy is initiated earlier in the course of disease. In the case of treatments for PD, this effect could be due to sensitization of striatal neurons or enhanced efficiency of dopaminergic release or other mechanisms, and cannot be entirely excluded in our trial. Another potential problem is differential dropout between groups. Subjects randomized to delayed treatment may drop out while they are still receiving placebo. Dropouts during this period would en-

hance apparent differences between groups. For this reason, we chose to analyze the 371 subjects who reached the active treatment phase in our primary analysis, rather than the original randomized cohort of 404 subjects.

Changes in total UPDRS score from baseline were 2.72 units for the group treated with rasagiline, 1 mg/d, for 1 year and 2.05 units for the group treated with rasagiline, 2 mg/d, for 1 year. These declines are somewhat smaller than the reported decline in treated patients in the DATATOP trial (4.6 units)¹⁶ and in the controlled trial of lazabemide (6.1 units).¹⁷ Whether the differences are due to methodological differences or the effects of rasagiline is unknown.

Rasagiline was well tolerated during the trial. During the placebo-controlled phase, adverse events were not more common in subjects receiving rasagiline than in those receiving placebo. Individual adverse experiences and serious adverse experiences were relatively uncommon in the active treatment phase of the trial as well, and were comparable to the first 6 months in overall frequency. Adverse events that are relatively frequent with other antiparkinsonian medications, including hallucinations, nausea, edema, and somnolence, were not common in this trial.

The results from the initial 6-month placebo-controlled phase of this study showed that rasagiline is well tolerated and exerts an antiparkinsonian effect in subjects with early mild PD. The randomized delayed-start analysis presented here suggests that the effects of rasagiline on the progression of disability in patients with PD cannot be fully explained by its symptomatic effect and may be due to a disease-modifying activity of the drug. Longer-duration studies are needed to confirm these findings.

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