ORIGINAL ARTICLE

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease

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ABSTRACT

BACKGROUND

A therapy that slows disease progression is the major unmet need in Parkinson's disease.

METHODS

In this double-blind trial, we examined the possibility that rasagiline has disease-modifying effects in Parkinson's disease. A total of 1176 subjects with untreated Parkinson's disease were randomly assigned to receive rasagiline (at a dose of either 1 mg or 2 mg per day) for 72 weeks (the early-start group) or placebo for 36 weeks followed by rasagiline (at a dose of either 1 mg or 2 mg per day) for 36 weeks (the delayed-start group). To determine a positive result with either dose, the early-start treatment group had to meet each of three hierarchical end points of the primary analysis based on the Unified Parkinson's Disease Rating Scale (UPDRS, a 176-point scale, with higher numbers indicating more severe disease): superiority to placebo in the rate of change in the UPDRS score between weeks 12 and 36, superiority to delayed-start treatment in the change in the score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72.

RESULTS

Early-start treatment with rasagiline at a dose of 1 mg per day met all end points in the primary analysis: a smaller mean (±SE) increase (rate of worsening) in the UPDRS score between weeks 12 and 36 (0.09±0.02 points per week in the early-start group vs. 0.14±0.01 points per week in the placebo group, P=0.01), less worsening in the score between baseline and week 72 (2.82±0.53 points in the early-start group vs. 4.52±0.56 points in the delayed-start group, P=0.02), and noninferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72 (0.085±0.02 points per week in the early-start group vs. 0.085±0.02 points per week in the delayed-start group, P<0.001). All three end points were not met with rasagiline at a dose of 2 mg per day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47±0.50 points in the early-start group and 3.11±0.50 points in the delayed-start group, P=0.60).

CONCLUSIONS

Early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not. Because the two doses were associated with different outcomes, the study results must be interpreted with caution. (ClinicalTrials.gov number, NCT00256204.)

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A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in Parkinson's disease.[1] Although current therapies provide beneficial effects on symptoms that help control the classic motor features of the disease (i.e., tremor, rigidity, and bradykinesia), intolerable disability eventually develops in most patients.[2] Numerous agents have neuroprotective effects in laboratory models, but none have been shown to have disease-modifying effects in patients with Parkinson's disease.[3] A limiting factor is the requirement for a clinical end point that reliably measures disease progression and is not confounded by the study intervention's effects on symptoms.

The delayed-start design was introduced to address this problem.[4,5] Delayed-start studies are conducted in two phases. In phase 1, subjects are randomly assigned to receive either active drug or placebo. Differences between groups at the end of this phase could be related to effects on symptoms, disease-modifying effects, or both. In phase 2, subjects in both groups receive the active drug. Persistent differences between the two groups at the end of phase 2 cannot be readily explained by effects on symptoms alone, since both groups are receiving the same treatment, and these differences are consistent with the possibility of a disease-modifying effect.

Rasagiline (*N*-propargyl-[1*R*]-aminoindan) (Azilect, Teva Pharmaceutical Industries) is an inhibitor of monoamine oxidase type B (MAO-B) that is approved for the symptomatic treatment of Parkinson's disease.[6-8] Rasagiline also provides neuroprotective effects in laboratory models of neurodegeneration.[9-12] In the present study, we used the delayed-start design to examine the potential disease-modifying effects of rasagiline in Parkinson's disease.[13]

METHODS

STUDY DESIGN

The Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) study was an 18-month, double-blind, placebo-controlled, multicenter trial that used a delayed-start design.[13] The study was performed in two phases, each lasting 36 weeks. In phase 1, subjects were randomly assigned to one of four study groups: rasagiline at a dose of either 1 mg or 2 mg per day (the early-start groups) or corresponding placebo. In phase 2, subjects in the early-start groups continued to receive their assigned treatment while subjects in the placebo groups switched to rasagiline at a dose of 1 mg or 2 mg per day (the delayed-start groups). Thus, the early-start groups received rasagiline (1 mg or 2 mg per day) for 72 weeks, and the delayed-start groups received placebo for 36 weeks followed by rasagiline (1 mg or 2 mg per day) for 36 weeks. No concomitant antiparkinsonian medication was permitted. If subjects required additional treatment during phase 1, they could proceed directly to phase 2. Subjects who required additional therapy in phase 2 were withdrawn from the study.

SUBJECTS

Men and women between 30 and 80 years of age who were not currently receiving treatment for Parkinson's disease were eligible for the study. The diagnosis of Parkinson's disease was based on the presence of at least two of the three cardinal features of the disease (resting tremor, bradykinesia, or rigidity); if resting tremor was not present, subjects had to have unilateral onset of symptoms. Subjects who had previously received any antiparkinsonian medication for more than 3 weeks or who had received rasagiline or selegiline (at any dose) or coenzyme Q_{10} (at more than 300 mg per day) within the previous 120 days were not eligible. Other exclusion criteria included a disease duration of more than 18 months since diagnosis, a Hoehn and Yahr stage of 3 or higher (scores in the Hoehn and Yahr staging system for Parkinson's disease range from 1 to 5, with higher scores indicating more severe disability), and atypical or secondary parkinsonism.

Visits were performed at baseline and at weeks 4, 12, 24, 36, 42, 48, 54, 60, 66, and 72. At each visit (except week 4), subjects were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS, which ranges from 0 to 176 and includes subscales of mental function, activities of daily living, and motor function, with higher scores indicating more severe disease).[14] Adverse events and vital signs were recorded at each visit. There was no restriction in dietary intake of tyramine, and certain antidepressant agents were allowed.

Teva Pharmaceutical Industries funded the study and was responsible for data collection, monitoring, and statistical analysis. The authors were responsible for the study design, interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for

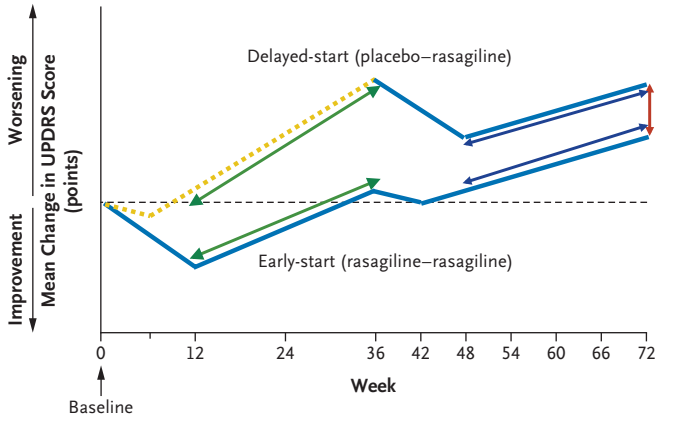


Figure 1. Schematic Illustration of the Three Primary End Points of the Study.
The three primary end points, which had to be met in a hierarchical fashion to declare positive results, are shown. The green arrows indicate the first end point: the superiority of early-start treatment versus placebo with respect to the estimate of the rate of change from baseline in the total Unified Parkinson's Disease Rating Scale (UPDRS) score between weeks 12 and 36. The red arrow indicates the second end point: the superiority of early-start treatment versus delayed-start treatment with respect to the estimate of change in the total UPDRS score between baseline and week 72. The blue arrows indicate the third end point: the noninferiority of early-start treatment as compared with delayed-start treatment with respect to the estimated rate of change from baseline in the slope for the total UPDRS score between weeks 48 and 72. The dashed yellow line indicates placebo, and the solid blue lines indicate rasagiline.

publication. The authors had complete access to the database, performed independent statistical analyses, and vouch for the completeness and accuracy of the data and data analysis.

STATISTICAL ANALYSIS

The primary analysis comprised three hierarchical end points based on the change from baseline in the total UPDRS score (Fig. 1). The first end point compared estimates of slope (the change in UPDRS points per week) between the rasagiline groups (1 mg or 2 mg per day) and placebo groups from weeks 12 through 36. This comparison determined whether there was a difference in the rate of disease progression, as reflected by the UPDRS score, between each rasagiline group and placebo after week 12, when it was assumed that the full effect of rasagiline on symptoms had been established. A disease-modifying agent would be expected to slow the rate of progression, as compared with placebo.

The second end point compared the estimated change in the total UPDRS score between baseline and week 72 in the early-start and delayed-start rasagiline groups (1 mg or 2 mg per day). This comparison determined whether the benefits observed in the early-start group at the end of phase 1 were still present at the end of the study, when subjects in the early-start and delayed-start groups were receiving the same treatment. Benefits of early-start treatment would be expected to persist if the treatment had a disease-modifying effect.

The third end point tested for the noninferiority of slope estimates for the rate of change from baseline in the UPDRS score between weeks 48 and 72 in the early-start groups as compared with the delayed-start groups. A noninferiority margin of 0.15 UPDRS points per week was prespecified. This end point was designed to determine whether the difference between the groups was enduring (as would be expected with a disease-modifying effect) and not diminishing (as would be expected with an agent that had a prolonged and cumulative effect on symptoms).

For each dose, all three end points had to be met to declare the study positive. The secondary end point was the change in the total UPDRS score between baseline and the last observed value in phase 1. The sample size was based on the calculation used in the Rasagiline (TVP-1012) in Early Monotherapy for Parkinson's Disease Outpatients (TEMPO) study (ClinicalTrials.gov number, NCT00203060).[15] This calculation indicated that 1100 subjects would be required to provide an 87% power to detect a difference of 1.8 UPDRS points between the early-start and delayed-start groups in the mean change in the UPDRS score from baseline to the average of the UPDRS scores from weeks 48 to 72, with an alpha level of 0.05 and a 15% dropout rate.

For the first primary end point, all subjects who underwent evaluations at baseline and week 12 or later were included in the analysis. For the second and third primary end points, all subjects who received at least 24 weeks of treatment during phase 1 and who underwent an evaluation at the week 48 visit or later were included. Safety assessments included all subjects who were randomly assigned to a study treatment.

Statistical analysis was performed with a mixed-model repeated-measures analysis of covariance that included the following fixed effects: treatment group, week in trial, week-by-treatment interaction, center, and total UPDRS score at baseline. The first end point was analyzed with the use of the combined placebo groups. For end points two and three, the model was fitted sepa-

rately for each dose because heterogeneous covariate effects were observed between the two doses. To maintain a type I error of 0.05 in the overall study, the hierarchical method was used to account for multiple primary end points for each dose and the Hochberg step-up Bonferroni method was used to account for testing of two doses[16]; this allowed for each dose to be tested separately. Various prespecified sensitivity and supportive analyses, including multiple imputation strategies, were used to validate the results and address the issue of missing data. For the secondary end point, an analysis-of-covariance model was used to assess the adjusted mean change in the total UPDRS score between baseline and the last observed value in phase 1.

To address the possibility that an effect on symptoms might mask a disease-modifying effect in this cohort of subjects with very mild disease, a post hoc subgroup analysis was conducted in subjects with high total UPDRS scores (i.e., the highest quartile of scores) at baseline.

RESULTS

CHARACTERISTICS OF THE SUBJECTS

A total of 1176 subjects were recruited from 129 centers in 14 countries, signed an informed-consent form approved by the local institutional review board, and were assigned to a treatment group according to a centralized, computer-generated randomization schedule (Fig. 2). A total of 1164 subjects (99%) were included in the first primary end-point analysis, and 996 subjects (85%) were included in the second and third primary end-point analyses. Baseline demographic and clinical characteristics are shown in Table 1. There were no significant differences among the treatment groups. The mean duration of disease from the time of diagnosis was 4.5 months, and the mean total UPDRS score was 20.4.

RESPONSES TO TREATMENT

Results of the three end points comprising the primary analysis and the secondary end point for each dose are shown in Table 2. For each dose, the mean change in the UPDRS score from baseline to each visit is shown in Figure 3.

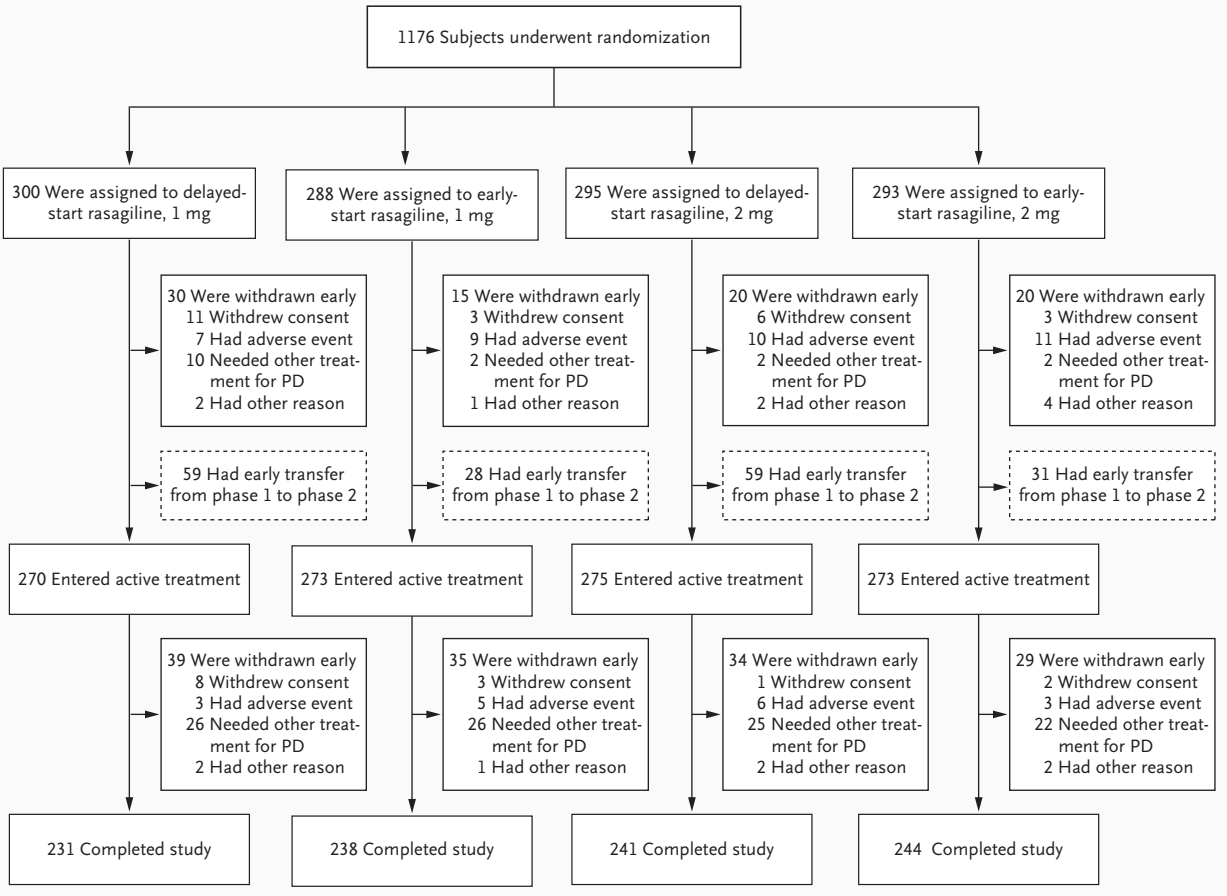
Among subjects who received rasagiline at a dose of 1 mg per day, the estimates of change in the slope of UPDRS scores per week between weeks 12 and 36 showed a slower rate of worsening (i.e., increase in the UPDRS score) for rasagiline (0.09±0.02 points per week) than for placebo (0.14±0.01 points per week) ($P=0.01$). The early-start group had less worsening in the mean total UPDRS score between baseline and week 72 (2.82±0.53 points) than the delayed-start group (4.50±0.56 points) ($P=0.02$). The estimates of the change in the UPDRS scores (slope) between weeks 48 and 72 showed noninferiority of the response in the early-start group (0.085±0.02 points per week) as compared with the response in the delayed-start group (0.085±0.02 points per week) ($P<0.001$). Thus, rasagiline at a dose of 1 mg per day met all three end points in the primary analysis. The model for the first primary end point assumed linearity in the rate of change in UPDRS points per week; results were confirmed by means of an alternative categorical model. The results of the second primary end point were confirmed by several predefined sensitivity and confirmatory analyses (Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

For the secondary end point (the change in the total UPDRS score between baseline and the last observed value in phase 1), rasagiline at a dose of 1 mg per day (1.26±0.36 points) was superior to placebo (4.27±0.26 points) ($P<0.001$).

Among subjects who received rasagiline at a dose of 2 mg per day, estimates of the rate of change in the UPDRS slope between weeks 12 and 36 showed less worsening in the rasagiline group (0.07±0.02 points per week) than in the placebo group (0.14±0.01 points per week) ($P<0.001$). However, the change in the total UPDRS score between baseline and week 72 in the early-start group (3.47±0.50 points) did not differ significantly from that in the delayed-start group (3.11±0.50 points) ($P=0.60$). The estimates of the rate of change in the UPDRS score between weeks 48 and 72 showed noninferiority of the response in the early-start group (0.094±0.01 points per week) as compared with the response in the delayed-start group (0.065±0.02 points per week) ($P<0.001$). Thus, rasagiline at a dose of 2 mg per day did not meet all three end points of the primary analysis, and the results were negative for this dose. For the secondary end point, rasagiline at a dose of 2 mg per day (1.11±0.36 points) was superior to placebo (4.27±0.26 points) ($P<0.001$).

POST HOC SUBGROUP ANALYSIS

To address the possibility that rasagiline at a dose of 2 mg per day had an effect on symptoms



Study Cohorts	Delayed-Start Rasagiline (1 mg)	Early-Start Rasagiline (1 mg)	Delayed-Start Rasagiline (2 mg)	Early-Start Rasagiline (2 mg)	All
			no. of participants		
Subjects who underwent randomization	300	288	295	293	1176
Efficacy cohort for first primary end point	295	286	293	290	1164
Efficacy cohort for second and third primary end points	238	251	249	258	996
Subjects in efficacy cohort for second and third primary end points who completed active phase	217	228	228	237	910

Figure 2. Randomization and Treatment of the Study Subjects.

The efficacy cohort for the first primary end point included subjects who were evaluated at baseline and at the week 12 visit or later. The efficacy cohort for the second and third primary end points included subjects who were evaluated for at least 24 weeks during the placebo-controlled phase and who underwent at least one evaluation at the week 48 visit or later. PD denotes Parkinson's disease.

that might have masked a disease-modifying benefit in subjects with very low UPDRS scores, the primary and secondary analyses were performed for subjects with total UPDRS scores in the highest quartile (>25.5 points) at baseline. Among subjects receiving 2 mg of rasagiline per day, the difference in the change in UPDRS scores from baseline to week 72 between the early-start and delayed-start groups was significantly greater among subjects with baseline UPDRS scores in the highest quartile than among subjects with scores in the other three quartiles ($P=0.03$). This

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Rasagiline, 1 mg/day		Rasagiline, 2 mg/day		
	Delayed-Start Group (N=300)	Early-Start Group (N=288)	Delayed-Start Group (N=295)	Early-Start Group (N=293)	Total (N=1176)
Age — yr	61.9±9.7	62.4±9.7	62.4±9.7	62.3±9.6	62.2±9.7
Time since diagnosis — mo	4.3±4.6	4.6±4.7	4.6±4.6	4.6±4.6	4.5±4.6
Male sex — %	62.0	60.8	61.7	59.7	61.1
Total UPDRS score (range, 0–176)†	20.2±8.8	20.6±8.4	19.9±8.1	20.8±8.8	20.4±8.5
Motor subscale (range, 0–108)	14.0±6.5	14.5±6.3	13.8±6.1	14.6±6.5	14.2±6.4
ADL subscale (range, 0–52)*	5.3±3.1	5.1±2.8	5.1±2.9	5.4±3.1	5.2±3.0
Hoehn and Yahr stage (range, 1–5)	1.51±0.5	1.53±0.5	1.46±0.5	1.52±0.5	1.51±0.5

* Plus–minus values are means ±SD. For all scales shown, higher scores indicate more severe parkinsonism. ADL denotes activities of daily living, and UPDRS Unified Parkinson's Disease Rating Scale.
† The total UPDRS score includes the scores of the mental, motor, and ADL subscales.

interaction suggests that these subgroups can be considered separately. Subjects with baseline UPDRS scores in the highest quartile who received either 1 mg or 2 mg of rasagiline per day met all three primary end points (Table 2a in the Supplementary Appendix). In the subgroup of 114 subjects with UPDRS scores in the highest quartile who received rasagiline at a dose of 2 mg per day, subjects in the early-start group had less worsening in the UPDRS score between baseline and week 72 than subjects in the delayed-start group (–3.63±1.72 points) (P=0.04). In the 105 subjects with UPDRS scores in the highest quartile at baseline who received rasagiline at a dose of 1 mg per day, subjects in the early-start group had less worsening in the total UPDRS score between baseline and week 72 than subjects in the delayed-start group (–3.40±1.66 points) (P=0.04). In the subgroup of subjects with UPDRS scores in the lower three quartiles (≤25.5 points) at baseline, neither dose met all three primary end points (Table 2b in the Supplementary Appendix).

ADVERSE EVENTS

Adverse events are listed in Table 3. One subject in the early-start group who received rasagiline at a dose of 1 mg per day had a melanoma at week 72. No subject had tyramine or serotonin reactions.

DISCUSSION

In this study, we used a delayed-start design to look for possible disease-modifying effects of rasagiline in early Parkinson's disease. Significant benefits had to be achieved in three hierarchical primary end points for results to be considered positive for either dose. There had to be less worsening in the rate of change in the UPDRS score between weeks 12 and 36 as compared with placebo, less worsening in the UPDRS score between baseline and week 72 in the early-start group than in the delayed-start group, and noninferiority with respect to the rate of change (worsening) in the UPDRS score between weeks 48 and 72 in the early-start group as compared with the delayed-start group. Rasagiline at a dose of 1 mg per day met all three predefined end points; rasagiline at a dose of 2 mg per day did not. Both doses of rasagiline had beneficial effects on symptoms, as compared with placebo, findings that are similar to those that have been reported previously.[6]

It is difficult to explain why the two doses (1 mg per day and 2 mg per day) did not provide similar results. There were no significant differences in baseline characteristics between the two rasagiline groups, nor was there a significant difference in dropout rates. In the laboratory, the protective effects of propargylamines are characterized by a U-shaped curve; that is, an increase or decrease in the concentration of the propargylamine can be associated with a loss of benefit.[17] However, these effects are observed with logarithmic changes, and it is difficult to imagine that protective effects could be lost with a mere doubling of the dose. A marked effect of the 2-mg dose on symptoms might have masked a benefit associated with early-start treatment in

Table 2. Results for the Primary and Secondary End Points.*

End Point	Estimated No. of Points	Confidence Interval†	P Value
First primary (estimated rate of change in UPDRS score/wk, wk 12–36)			
Placebo	0.14±0.01		
Rasagiline			
1 mg/day	0.09±0.02		
2 mg/day	0.07±0.02		
1 mg/day vs. placebo	–0.05±0.02	–0.08 to –0.01	0.01
2 mg/day vs. placebo	–0.07±0.02	–0.11 to –0.04	<0.001
Second primary (estimated change in total UPDRS score from baseline to wk 72)			
Rasagiline			
1 mg/day, early start	2.82±0.53		
1 mg/day, delayed start	4.50±0.56		
2 mg/day, early start	3.47±0.50		
2 mg/day, delayed start	3.11±0.50		
1 mg/day, early start vs. delayed start	–1.68±0.75	–3.15 to –0.21	0.02
2 mg/day, early start vs. delayed start	0.36±0.68	–0.99 to 1.70	0.60
Third primary (estimated rate of change in UPDRS score/wk, wk 48–72)			
Rasagiline			
1 mg/day, early start	0.085±0.02		
1 mg/day, delayed start	0.085±0.02		
2 mg/day, early start	0.094±0.01		
2 mg/day, delayed start	0.065±0.02		
1 mg/day, early start vs. delayed start	0.00±0.02	–0.04 to 0.04‡	<0.001
2 mg/day, early start vs. delayed start	0.03±0.02	–0.01 to 0.06‡	<0.001
Secondary (change in total UPDRS score from baseline to final visit in phase 1)			
Placebo	4.27±0.26		
Rasagiline			
1 mg/day	1.26±0.36		
2 mg/day	1.11±0.36		
1 mg/day vs. placebo	–3.01±0.43	–3.86 to –2.15	<0.001
2 mg/day vs. placebo	–3.15±0.43	–4.00 to –2.31	<0.001

* Plus–minus values are means ±SE. For each between-group comparison, the value shown is the estimated change in the first group minus the estimated change in the second group. A total of 1164 subjects were included in the first primary end-point analysis, and 996 subjects were included in the second and third primary end-point analyses. UPDRS denotes Unified Parkinson's Disease Rating Scale.

† Confidence intervals are at the 95% level unless otherwise noted.

‡ Noninferiority of the slope in the early-start group as compared with the slope in the delayed-start group was achieved if the upper limit of the one-sided 95% CI (i.e., a 90% CI) for the difference in slopes did not cross the margin of 0.15 points in the score on the UPDRS per week.

this population of patients with very mild disease. Indeed, for rasagiline at a dose of 2 mg, a post hoc subgroup analysis showed that for subjects in the highest quartile of UPDRS scores at baseline, early-start rasagiline provided a significant benefit over delayed-start rasagiline with respect to the change in the UPDRS score between baseline and 72 weeks (–3.63 UPDRS points), and all primary end points were met despite the relatively small sample. Furthermore, at a dose

of 2 mg per day, early-start treatment with rasagiline was superior to delayed-start rasagiline in the TEMPO study, in which subjects had relatively high UPDRS scores at baseline (mean, 25.0 points).[15] Similar findings were observed in subjects in the highest quartile of UPDRS scores who received rasagiline at a dose of 1 mg per day.

These observations are consistent with the hypothesis that the effects on symptoms associated with the dose of 2 mg per day may have masked disease-modifying effects in this population of subjects with very mild disease. Since this explanation is primarily supported by a post hoc analysis, it cannot be considered to be conclusive, and we cannot rule out the possibility that the findings with rasagiline at a dose of 1 mg per day represent false positive results rather than that the findings with 2 mg per day represent false negative results. In future delayed-start studies, it might be worthwhile to include subjects with slightly more advanced disease.

Although the study results were not consistent for the two doses, they provide support for the possibility that rasagiline at a dose of 1 mg per day has a disease-modifying effect, since at this dose, early treatment is associated with less worsening in the UPDRS score than delayed treatment. This effect cannot be readily explained by an effect on symptoms alone, since both groups received the same treatment for the last 9 months of the study. It is theoretically possible that these results are due to an effect on symptoms that evolves over a prolonged period of time, but this explanation seems unlikely, given that there was no indication that the slopes in the early-start and delayed-start groups were converging after 9 months of treatment.

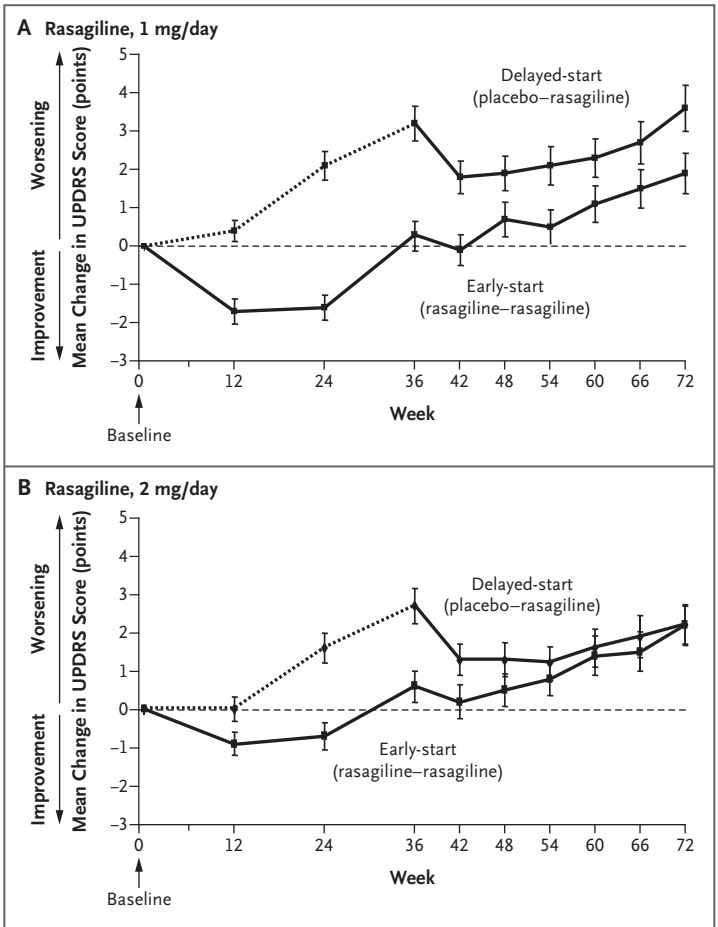


Figure 3. Changes in Scores on the Unified Parkinson's Disease Rating Scale (UPDRS) in the Four Study Groups.

The mean (±SE) change from baseline in the UPDRS score in the efficacy cohort for the second and third primary end points for patients receiving rasagiline at a dose of 1 mg per day (Panel A) and those receiving 2 mg per day (Panel B) are shown. The dashed lines indicate placebo, and the solid lines indicate rasagiline.

The possibility that rasagiline might have a neuroprotective effect is supported by laboratory studies showing that the drug, and its metabolite 1-(R)-aminoindan, have antiapoptotic effects and protect neurons from a variety of toxins in various models.[9-12,18-20] Neuroprotection in these models appears to be related to a propargyl ring incorporated within the rasagiline molecule rather than to MAO-B inhibition.[20,21] Other MAO-B inhibitors and propargylamines have been tested for disease-modifying effects in Parkinson's disease. Several trials have shown positive results with selegiline, but a confounding effect of the drug on symptoms could not be ruled out.[22,23] Conversely, a trial of TCH346 showed negative results, but the correct dose may not have been used.[24] Although neuroprotection is a plausible explanation for the results seen with rasagiline at a dose of 1 mg per day, alternative mechanisms could account for positive results in a delayed-start study. These mechanisms include preservation of a beneficial compensatory response that, once lost, cannot be restored and prevention of a maladaptive compensatory response that, once established, cannot be reversed. Indeed, it has been proposed that early introduction of any agent that affects symptoms could influence compensatory responses and provide long-term benefits as compared with later introduction of the same agent.[25]

There are several possible concerns with the

delayed-start design[26] and with this trial specifically. First, a high dropout rate during the placebo phase could confound the results by disproportionately affecting subjects in the delayed-start group. However, we were able to maintain a relatively low dropout rate, and the results were confirmed by multiple sensitivity analyses that included a variety of imputation strategies. Second, patients in this study had very early disease, and there was a risk of misdiagnosis in such a population. However, randomization should have distributed these subjects equally among the treatment groups. Third, we used the slope estimate for the change in the UPDRS score as the first hierarchical end point, although this end point has not been used before in studies of Parkinson's disease, and there is no assurance that the worsening in UPDRS scores is linear. However, the results were positive and confirmed by an alternative categorical

Table 3. Adverse Events, According to Treatment Group.*

Event	Placebo†	Rasagiline, 1 mg/day	Rasagiline, 2 mg/day
		no./total no. (%)	
In >5% of subjects in any group, placebo phase			
Headache	37/595 (6.2)	14/288 (4.9)	15/293 (5.1)
Back pain	32/595 (5.4)	14/288 (4.9)	15/293 (5.1)
Depression	36/595 (6.1)	10/288 (3.5)	10/293 (3.4)
Nasopharyngitis	32/595 (5.4)	12/288 (4.2)	11/293 (3.8)
Anxiety	34/595 (5.7)	10/288 (3.5)	9/293 (3.1)
Fatigue	17/595 (2.9)	17/288 (5.9)	10/293 (3.4)
Related to dopaminergic therapy, placebo phase			
Nausea or vomiting	23/595 (3.9)	12/288 (4.2)	8/293 (2.7)
Hypertension	23/595 (3.9)	5/288 (1.7)	7/293 (2.4)
Somnolence	9/595 (1.5)	2/288 (0.7)	4/293 (1.4)
Orthostatic hypotension	5/595 (0.8)	2/288 (0.7)	1/293 (0.3)
Hallucination	1/595 (0.2)	0/288	1/293 (0.3)
Hypersexuality	0/595	0/288	1/293 (0.3)
In >5% of subjects in any group, active phase			
Falls			
Delayed start		16/270 (5.9)	17/275 (6.2)
Early start		13/273 (4.8)	15/273 (5.5)
Back pain			
Delayed start		15/270 (5.6)	11/275 (4.0)
Early start		21/273 (7.7)	10/273 (3.7)
Nasopharyngitis			
Delayed start		11/270 (4.1)	18/275 (6.5)
Early start		14/273 (5.1)	12/273 (4.4)
Arthralgia			
Delayed start		14/270 (5.2)	10/275 (3.6)
Early start		14/273 (5.1)	15/273 (5.5)
Headache			
Delayed start		15/270 (5.6)	15/275 (5.5)
Early start		13/273 (4.8)	8/273 (2.9)
Musculoskeletal pain			
Delayed start		6/270 (2.2)	15/275 (5.5)
Early start		5/273 (1.8)	9/273 (3.3)

Table 3. (Continued.)

Event	Placebo†	Rasagiline, 1 mg/day	Rasagiline, 2 mg/day
		no./total no. (%)	
Related to dopaminergic therapy, active phase			
Nausea or vomiting			
Delayed start		11/270 (4.1)	11/275 (4.0)
Early start		7/273 (2.6)	9/273 (3.3)
Hypertension			
Delayed start		4/270 (1.5)	4/275 (1.5)
Early start		7/273 (2.6)	8/273 (2.9)
Orthostatic hypotension			
Delayed start		4/270 (1.5)	6/275 (2.2)
Early start		5/273 (1.8)	4/273 (1.5)
Somnolence			
Delayed start		1/270 (0.4)	3/275 (1.1)
Early start		4/273 (1.5)	2/273 (0.7)
Hallucination			
Delayed start		2/270 (0.7)	2/275 (0.7)
Early start		1/273 (0.4)	2/273 (0.7)
Hypersexuality			
Delayed start		0/270	0/275
Early start		0/273	0/273

* There were no significant differences in adverse events among the study groups.
† The two placebo groups were combined for this analysis.

analysis. Finally, the placebo phase could have been too short to permit a disease-modifying effect to occur. However, we did see a benefit with 1 mg of rasagiline per day, and giving placebo to subjects with Parkinson's disease for longer than 9 months would probably result in an unacceptable dropout rate. The clinical significance of a difference of 1.7 points in the UPDRS score between the early-start and delayed-start groups that received rasagiline at a dose of 1 mg per day is not known, but it does represent a 38% reduction in the degree of change from baseline. Furthermore, the UPDRS is a relatively insensitive measure in subjects with early disease and may not capture improvement in nonmotor areas.[27]

It is important to consider the clinical consequences of this study. From a practical point of view, the study findings suggest a possible benefit of the early use of rasagiline at a dose of 1 mg per day; however, given the negative findings for the 2-mg dose, we cannot definitively conclude that rasagiline at a dose of 1 mg per day has disease-modifying effects. It will be important to determine whether these results can be confirmed and whether benefits seen at 18 months will endure and translate into reduced cumulative disability in clinically meaningful areas such as impairment of gait and balance and cognitive dysfunction.

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