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Rasagiline Improves Quality of Life in Patients With Early Parkinson's Disease

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Abstract: The objective of this study was to determine the effects of rasagiline as monotherapy on quality of life (QOL) in patients with early Parkinson's disease (PD). Rasagiline, a potent, second-generation, irreversible, selective monoamine oxidase B inhibitor improves PD symptoms in patients with early PD. Patients with early untreated PD were randomly assigned to once-daily rasagiline 1 mg/day, rasagiline 2 mg/day, or placebo in a 6-month, double-blind trial (n = 404). At the end of 6 months, patients entered the preplanned, active-treatment phase in which those receiving 1 mg/day and 2 mg/day of rasagiline continued on their previously assigned dosages and those receiving placebo switched to rasagiline 2 mg/day, while maintaining blinding to treatment assignments. QOL was measured with the Parkinson's Disease Quality of Life questionnaire (PDQUALIF) at 0, 14, 26, and 52 weeks after randomization. Analysis of the change in PDQUALIF scores from baseline to 6 months showed adjusted treatment effects (with 95% confidence interval) favoring rasagiline over placebo of −2.91 units (−5.19, −0.64, $P = 0.01$) for the 1 mg/day group and −2.74 units (−5.02, −0.45, $P = 0.02$) for the 2 mg/day. Subscore analysis attributed most of this benefit to the self-image/sexuality domain. At 12 months (n = 266), with all groups receiving rasagiline for at least 6 months, no significant differences in PDQUALIF scores were seen between groups. Rasagiline improved QOL compared with placebo. This QOL improvement appears to be accounted for primarily by the symptomatic benefit of rasagiline. © 2006 Movement Disorder Society

Key words: Parkinson's disease; rasagiline; quality of life

There has been a recent increase in the use of quality of life (QOL) measures as outcomes to assess the efficacy of interventions in Parkinson's disease (PD) clinical trials.[1–3] This strategy reflects the realization that PD is a multidimensional disease resulting in progressive disability and QOL impairment.[4–6] Traditionally, motor outcomes have been the main tools used to measure treatment efficacy; however, motor, behavioral, and social factors all appear to be important determinants of QOL in PD.[7,8] In addition, whereas select interventions may positively impact motor outcomes, they may simultaneously cause nonmotor complications that can have a detrimental effect on QOL. Therefore, a more complete understanding of the impact of an intervention on the whole individual is obtained through QOL outcomes.

Rasagiline (*N*-propargyl-1(R)-aminoindan; TVP-1012) mesylate is a novel, selective, and potent irreversible inhibitor of monoamine oxidase type B (MAO-B).[9] In the TEMPO study, patients receiving either 1 mg/day or 2

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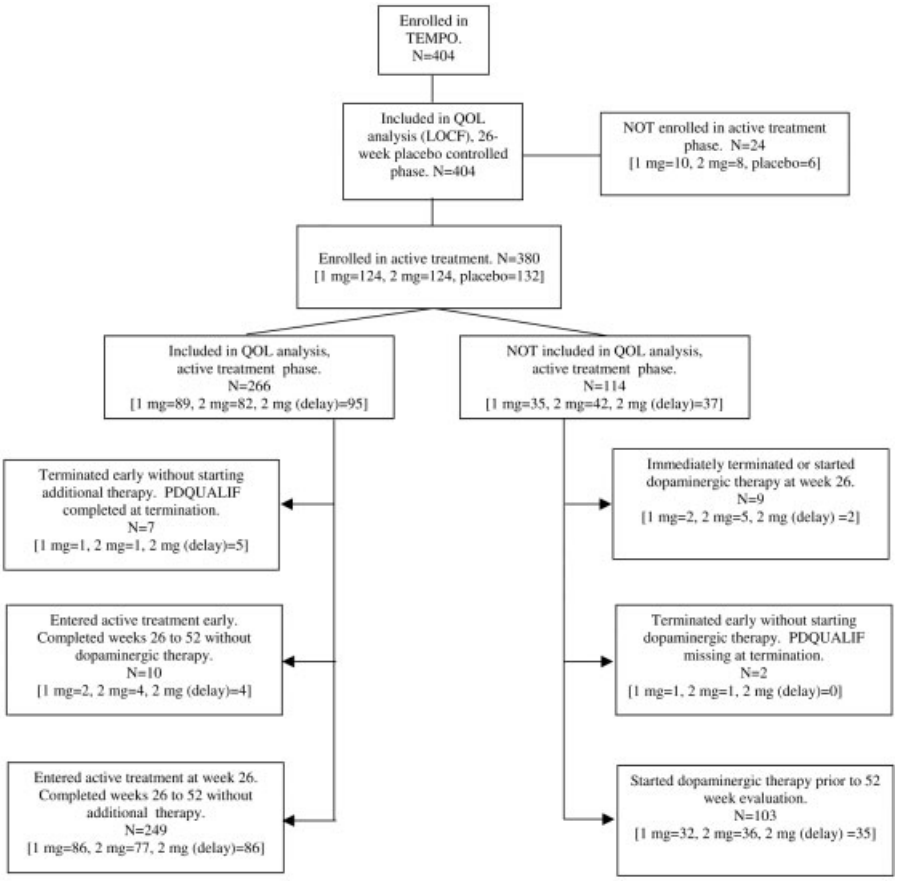

FIG. 1. Patient flow through quality of life (QOL) analysis. LOCF, last observation carried forward; PDQUALLIF, Parkinson's Disease Quality of Life questionnaire.

mg/day of rasagiline had better function, as measured by the Unified Parkinson Disease Rating Scale[10] (UPDRS), after 26 weeks of treatment compared to those receiving placebo.[11] A preplanned, 6-month, double-blind, active-treatment phase followed this 26 week, placebo-controlled phase, in which patients initially randomly assigned to placebo began taking rasagiline and those randomly assigned to rasagiline continued on their originally assigned treatment. Patients initially randomly assigned to rasagiline 1 and 2 mg/day continued to show better function on the UPDRS at the end of the 52-week study than patients for whom rasagiline treatment was delayed by 6 months, suggesting a possible disease modifying effect of rasagiline.[12] We now report on the quality of life outcomes in both the randomized, placebo-controlled, and the active-treatment phases of this study.

PATIENTS AND METHODS

Patients

Between November 1997 and June 1999, 404 eligible patients were enrolled at 32 sites. Eligibility criteria have been published previously.[11] All patients were included in the analysis of the QOL data for the initial placebo-controlled phase of the trial. Of the 380 patients who entered the active-treatment phase, only those who did not require supplemental dopaminergic therapy and who completed a QOL assessment at termination were included in the QOL analysis (n = 266). Figure 1 details the breakdown of subjects by whether they required additional therapy and whether they completed a QOL assessment at termination.

Study Design and Treatments

The TEMPO study was organized by the Parkinson Study Group (PSG) and sponsored by Teva Pharmaceutical Industries, Ltd. (Netanya, Israel) and Teva Neuroscience, Inc. (North Wales, PA). The study used a randomized delayed-start design, details of which have been previously published.[12] After informed consent was obtained, patients were randomly assigned to one of three treatment groups: (1) rasagiline 1 mg/day for 1 year, (2) rasagiline 2 mg/day for 1 year, or (3) matching placebo for 6 months followed by rasagiline 2 mg/day for 6 months.

After 26 weeks in the placebo-controlled phase, patients entered the active-treatment phase. Patients who were originally assigned to placebo were switched in a blinded manner to rasagiline 2 mg/day, whereas those originally assigned to rasagiline continued in a blinded manner on their previously assigned dosage.

Alternatively, patients could enter the active-treatment phase of the study at any time during the first 26 weeks in the case of emergence of disability requiring additional dopaminergic treatment. Under these circumstances, patients in the active-treatment arms continued on their assigned dosage, whereas patients in the placebo arm began rasagiline 2 mg/day. If patients required supplementary therapy after entering the active-treatment phase, additional dopaminergic therapy was initiated and the last available observation was carried forward for the week 52 visit.

Assessments

In addition to the safety and efficacy assessments described in detail previously,[11] patients completed the Parkinson Disease Quality of Life Questionnaire[13] (PDQUALIF) at baseline and at three of the study's eight follow-up visits (weeks 14, 26, and 52 weeks after randomization). The PDQUALIF is a validated self-administered disease-specific QOL scale consisting of 32 questions scored on a 5-point Likert scale. Responses to some questions are inverted, and the total score was then calculated as the sum of the 32 individual items on the questionnaire (score ranging from 0 to 128), with higher scores signifying worse quality of life. Seven domain subscores were calculated: social role, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function. An additional question (Question 33) compares current PD symptoms to 3 months ago using a five-point Likert scale (much better to much worse) and is not included in the total PDQUALIF score.

Statistical Analysis

The primary analysis focused on the 26-week placebo-controlled phase, which included an analysis of all 404 subjects initially randomized. During the first 26-week placebo-controlled phase, PDQUALIF scores were carried forward to week 26 for patients entering the active-treatment phase early. The changes from baseline to 26 weeks on the total, subscores, and individual items of the PDQUALIF were compared between the 1 mg/day and placebo groups and the 2 mg/day and placebo groups using analysis of covariance (ANCOVA). The model included treatment, center, treatment by center interaction (if significant at $P < 0.05$), and the comparable baseline score from the PDQUALIF. Missing PDQUALIF data for the first 26 weeks was assessed using the last observation carried forward (LOCF).

In the active-treatment phase, QOL was measured at only one visit (week 52). Patients who initiated dopaminergic therapy at any point or who terminated without initiating therapy but did not complete a final PDQUALIF assessment were not included in this analysis. The changes from baseline to 52 weeks on the total and subscores on the PDQUALIF were compared between the treatment groups as described for the placebo-controlled phase.

Kruskal–Wallis tests and χ^2 tests were used to compare baseline characteristics of subjects available for the QOL analyses in the active-treatment phase (n = 266) with those of subjects not available for these analyses (n = 114), as well as to compare baseline characteristics by treatment group for those included in the QOL analyses. Correlations between the baseline PDQUALIF scores and the UPDRS (Total, Mental, Motor, and Activities of Daily Living [ADL]) and Schwab and England ADL (SEADL) were calculated using Pearson's coefficients. Correlations of the changes from baseline to 26 weeks and 52 weeks between the PDQUALIF and the changes in the UPDRS (Total, Mental, Motor, and ADL) and SEADL over the same time periods were calculated similarly.

All statistical analyses were performed according to the intention-to-treat principle. All tests were two-tailed, with an overall significance level of 5% used for formal significance testing.

RESULTS

Progress Through the Study

The patient flow through the study is detailed in Figure 1. All enrolled patients (n = 404) were included in the 26-week evaluation of QOL in the placebo-controlled phase of the trial. Of the 380 patients enrolled in the active-treatment phase, only 266 completed a PDQUALIF after week 26 and, therefore, were included in the QOL analyses. There was no significant difference in the proportion of patients in each treatment group who were included in the QOL analysis during the active-treatment phase ($P = 0.52$).

Baseline Characteristics

Treatment groups were similar in all relevant clinical characteristics at baseline and reflected the relatively mild disease stage of the 404 participants.[11] Baseline mean PDQUALIF scores were slightly worse in the 2 mg/day rasagiline group (mean, 30.2) compared with the

TABLE 1. *Baseline characteristics: available vs. not available for QOL analysis in the active-treatment phase*

	Available QOL (n = 266)			Not available QOL (n = 114)		
	1 mg/day	2 mg/day	2 mg delay	1 mg/day	2 mg/day	2 mg delay
Age (yr)	60.8 (9.9)	61.7 (11.0)	60.4 (10.7)	61.6 (10.8)	57.1 (11.7)	60.1 (11.2)
Disease duration (yr)	1.0 (1.4)	1.1 (1.2)	1.0 (1.2)	0.8 (0.9)	1.3 (1.4)	0.8 (0.9)
Male sex, n (%)	59 (66)	47 (57)	63 (66)	25 (71)	24 (57)	26 (70)
White race, n (%)	82 (92)	80 (98)	90 (95)	34 (97)	42 (100)	33 (89)
Total UPDRS score	23.0 (11.7)	23.4 (8.9)	21.1 (8.5)	28.4 (10.1)	29.4 (9.6)	30.5 (13.4)
Motor subscale	16.3 (8.9)	16.2 (7.0)	15.1 (6.8)	21.0 (8.6)	20.7 (7.9)	21.6 (9.9)
ADL subscale	5.8 (3.6)	6.3 (3.2)	5.4 (2.8)	6.4 (3.0)	7.2 (3.2)	7.6 (3.9)
Mental subscale	0.9 (1.1)	1.0 (1.1)	0.6 (0.8)	0.9 (1.1)	1.5 (1.3)	1.2 (1.5)
SEADL	92.1 (6.0)	91.3 (5.3)	91.9 (5.7)	92.6 (5.1)	89.3 (6.8)	90.4 (7.0)
HY stage, median (range)	1.8 (0.5)	1.8 (0.5)	1.8 (0.5)	1.9 (0.5)	2.0 (0.5)	2.0 (0.4)
	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,2.5)	2 (1,3)	2 (1,3)
PDQUALIF score	27.1 (15.6)	25.5 (16.2)	24.6 (14.8)	29.6 (13.4)	37.0 (15.3)	31.7 (15.7)
Beck Depression Inventory	2.2 (2.3)	2.4 (2.7)	2.3 (2.6)	2.5 (2.7)	3.8 (2.9)	3.2 (3.0)

Data presented as mean (SD) or number (%) as appropriate.

QOL, quality of life; UPDRS, Unified Parkinson's Disease Rating Scale; SEADL, Schwab and England Activities of Daily Living; PDQUALIF, Parkinson's Disease Quality of Life questionnaire.

1 mg/day (mean, 28.3) and placebo groups (mean 26.9), although differences were not significant ($P = 0.29$).

Table 1 shows the baseline characteristics by treatment assignment for patients who had available data for the QOL analysis in the active-treatment phase and those who terminated or started dopaminergic therapy. Patients included in the QOL analysis were not significantly different in age, race, gender, or disease duration from those who were not included. However, those included in the 52-week analysis were less impaired, with significantly lower scores on the UPDRS ($P < 0.0001$) and its components. Among those included in the QOL analysis, there were no significant baseline differences by treatment group.

Analysis of QOL Outcomes

Placebo-Controlled Phase.

Figure 2 illustrates the total PDQUALIF scores by treatment assignment during the placebo-controlled phase. QOL improved from baseline in both groups receiving rasagiline over the initial 26 weeks and improvements were already notable at 14 weeks. In contrast, QOL steadily worsened in patients receiving placebo over the 26 weeks of assessment.

The adjusted mean change from baseline on the PDQUALIF (LOCF) was −0.36 for the 1 mg/day group, −0.19 for the 2 mg/day group, and +2.55 for the placebo group. The difference between the adjusted change scores for each rasagiline group versus placebo was significant (1 mg/day vs. placebo, $P = 0.01$; 2 mg/day vs. placebo, $P = 0.02$). No difference was noted between the two rasagiline arms ($P = 0.88$). The treatment effects (i.e., the difference in adjusted change scores between each active-treatment arm and placebo) favored rasagiline and were −2.91 (95% confidence interval [CI]: −5.19, −0.64; $P = 0.01$) for 1 mg/day versus placebo and −2.74 (95% CI: −5.02, −0.45; $P = 0.02$) for 2 mg/day versus placebo.

Analysis of the PDQUALIF subscores (Table 2) revealed that differences in the self-image/sexuality and, to a lesser extent, the social role domains drove the difference noted in the total score. The self-image/sexuality domain consists of seven items that assess the effect PD symptoms have on communication, intimacy, sexual desirability, and family roles. In addition, we compared the 145 subjects treated with rasagiline whose PDQUALIF improved during the placebo-controlled phase with the 61 subjects on placebo whose PDQUALIF improved; the subscore analysis mirrors the results for the entire cohort (data not shown).

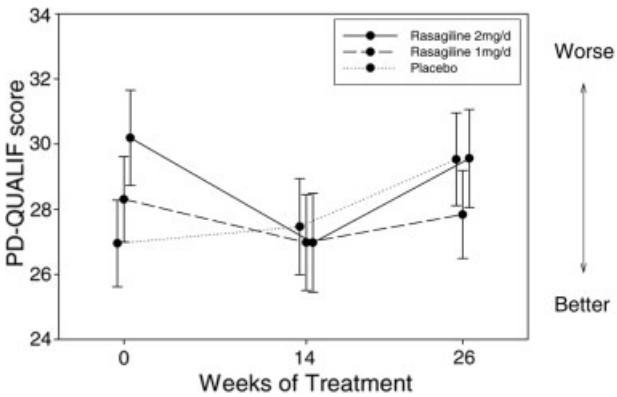

FIG. 2. Total quality of life (QOL) score by visit; placebo controlled phase (n = 404). PDQUALLIF, Parkinson's Disease Quality of Life questionnaire.

TABLE 2. *Analysis of variance for change from baseline analysis at 26 and 52 weeks*

	26 Weeks (n = 404)				52 Weeks (n = 266)			
	1 mg vs. placebo		2 mg vs. placebo		1 mg vs. 2 mg (delay)		2 mg vs. 2 mg (delay)	
	Rx effect	*P*	Rx effect	*P*	Rx effect	*P*	Rx effect	*P*
Total PDQUALIF	−2.91	**0.01**	−2.74	**0.02**	−0.27	0.85	1.74	0.25
Social role	−0.82	0.10	−0.98	**0.05**	−0.11	0.86	0.44	0.49
Self image/sexuality	−1.63	**0.0001**	−1.12	**0.008**	−0.42	0.42	0.43	0.42
Sleep	−0.07	0.69	0.02	0.92	−0.20	0.34	−0.02	0.94
Outlook	−0.23	0.34	−0.21	0.39	0.15	0.61	0.51	0.10
Physical function	−0.14	0.52	−0.15	0.48	0.13	0.65	0.55	0.06
Independence	−0.13	0.43	−0.08	0.63	0.53	**0.02**	−0.14	0.54
Urinary function	0.14	0.39	0.00	0.99	0.05	0.81	−0.03	0.88

The Rx effect is treatment effect (difference in adjusted change from baseline on the PDQUALIF between treatment groups). Negative numbers favor 1 mg or 2 mg over placebo/2 mg (delay) groups. Bolded items indicate statistically significant differences.

PDQUALIF, Parkinson's Disease Quality of Life questionnaire.

Active Treatment Phase.

Figure 3 shows the change from baseline on total PDQUALIF scores for each visit over the entire 52 weeks of the study (placebo-controlled and active-treatment phases) for the 249 patients who were included in the QOL analysis at 52 weeks and who completed all 52 weeks of the study. During the active-treatment period, patients in both early treatment arms slowly worsened, whereas the delayed 2-mg group showed improvement in QOL upon initiation of rasagiline treatment. This improvement in the delayed treatment arm is a replication of the effect observed in the placebo-controlled phase for the two active groups, confirming the robustness of the effect observed in the first phase.

All treatment arms slightly worsened from baseline to 52 weeks on the PDQUALIF. The adjusted mean change from baseline was +0.27, +2.28, +0.54 for the 1 mg/day, 2 mg/day, and 2 mg delay groups, respectively. Neither the treatment differences between the 1 mg/day and 2 mg delay groups nor the differences between the 2 mg/day and 2 mg delay groups was significant between baseline and 52 weeks (Table 2).

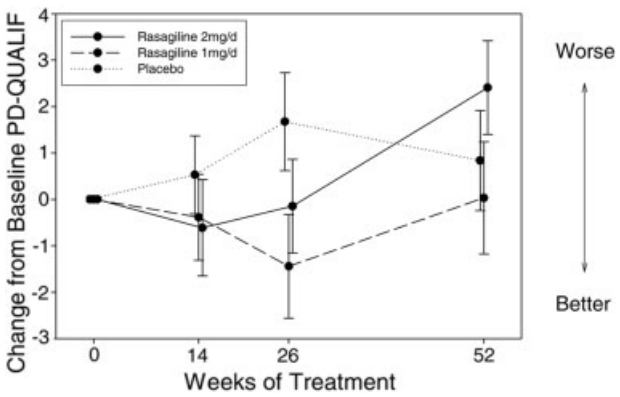

FIG. 3. Quality of life (QOL) change from baseline; active extension cohort (n = 249). Individuals initially randomized to placebo began active treatment with rasagiline at 26 weeks. PDQUALLIF, Parkinson's Disease Quality of Life questionnaire.

Correlations of QOL with UPDRS and Schwab and England ADL Scales

Table 3 outlines the correlations of the PDQUALIF baseline and change scores at 26 and 52 weeks with those on the UPDRS Total; UPDRS Motor, Mental, and ADL subscores; and the SEADL. Baseline PDQUALIF scores were highly correlated with baseline UPDRS and ADL scores. However, the changes in PDQUALIF at 26 weeks and 52 weeks were only weakly correlated with changes in UPDRS and SEADL scores over the same time period, and no relationship was seen between change in motor scores and change in PDQUALIF scores at 52 weeks.

DISCUSSION

Treatment with rasagiline in early PD results in significant improvement in QOL compared to placebo at 26 weeks. This early QOL improvement may result from a symptomatic benefit and/or disease modifying effect of rasagiline in early PD. However, unlike the positive impact noted on UPDRS scores at 12 months in patients treated with rasagiline early versus those treated later,[12] no such difference between early and delayed groups was seen on the QOL measure. This finding is probably because QOL measures are not sensitive enough to detect relative changes in disease progression over a 1-year period of time, which is supported by the relatively small deterioration in QOL in the placebo group during the first 26-week period. Alternatively, the QOL benefit of rasagiline may be through mechanisms unrelated to disease progression.

TABLE 3. *Correlations of QOL scores with disease severity*

	Baseline scores (N = 404)		Changes from baseline to 26 weeks (LOCF), N = 404		Changes from baseline to 52 weeks (N = 266)	
Variable	r	*P*	r	*P*	r	*P*
Total UPDRS	0.51	<0.0001	0.25	<0.0001	0.16	0.01
Motor UPDRS	0.34	<0.0001	0.13	0.01	0.08	0.22
Mental UPDRS	0.49	<0.0001	0.23	<0.0001	0.23	0.0002
ADL UPDRS	0.62	<0.0001	0.30	<0.0001	0.21	0.0006
SEADL	−0.56	<0.0001	−0.16	0.0009	−0.23	0.0001

r indicates Pearson's correlation coefficient.

QOL, quality of life; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living; SEADL, Schwab and England ADL.

Subscale analysis of the PDQUALIF revealed that the self-image/sexuality and social role domains seemed to drive the QOL improvement noted during the placebo-controlled phase. This effect on self-image may derive from a potential antidepressant effect of rasagiline by means of MAO inhibition, although mood was not systematically evaluated during the course of this study. In addition, the social role domain, second only to the physical domain, has been most well-correlated with disease severity in PD.[13] Any intervention that lessens disease severity might be expected to have a relatively larger influence on the social role domain. Therefore, the improvement noted in the social role domain may be accounted for, at least partially, by rasagiline's impact on disease severity. In addition, the subgroup analysis of subjects whose QOL scores improved, paralleled the whole group comparisons, suggesting the benefit of rasagiline on these subscores is likely to reflect an effect of rasagiline and not merely a nonspecific effect of QOL improvement in patients with early PD.

QOL was not measured between weeks 26 and 52. Therefore, there were no QOL data to carry forward (LOCF) for 114 patients who either initiated dopaminergic therapy or terminated for other reasons before 52 weeks, making analysis of the QOL outcome in the active-treatment phase subject to bias. Bias associated with nonrandom termination (i.e., patients with more severe disease and worse QOL being more likely to initiate dopaminergic therapy or terminate early) likely influenced the analysis of the active-treatment phase. In fact, patients not included in the 52-week QOL analysis did have worse baseline UPDRS and PDQUALIF scores than those who completed the active-treatment phase; and almost all of these patients (97) were excluded from the analysis for initiating dopaminergic therapy before 52 weeks.

Despite these caveats, certain findings in the active-treatment phase deserve additional attention. Patients randomly assigned to the delayed rasagiline arm stabilized and slightly improved in their QOL scores with the initiation of rasagiline at 26 weeks, replicating the results seen in the rasagiline-treated subjects during the first phase of the study. In fact, changes from baseline on QOL scores were no different between the early treatment groups and the delayed treatment group, suggesting that most of the beneficial effect of rasagiline on QOL in this study was through a symptomatic effect and not a disease modifying one. However, the study may not have had sufficient power to detect a disease modifying effect on QOL outcomes (in fact, the study was not powered to do so) or 6 months of treatment may not be long enough for meaningful differences in QOL outcomes to emerge.[11] Finally, missing data may have biased the results of the QOL analysis, although the direction of such bias is unknown.

Baseline measures of disease severity and function correlated with baseline PDQUALIF scores, further validating this QOL scale. This relationship between disease severity, function, and QOL has been shown in previous cross-sectional and longitudinal observational studies.[13–18] However, the responsiveness of QOL to a therapeutic intervention in a controlled trial in early PD has not been demonstrated previously. The change in QOL over the course of the study only weakly correlated with changes in measures of disease severity and did not correlate with change in motor function over the 52 weeks. Therefore, the effects of rasagiline on QOL coincide with but are not fully explained by the observed improvement in PD features as measured by UPDRS. This observation suggests that rasagiline has benefits beyond those captured by the UPDRS. This suggestion is supported by studies that show depression, social function, pain, and other nonmotor symptoms to be the largest determinants of QOL in PD.[4,7,8,19,20] How rasagiline influences QOL after more than 52 weeks independent of its influence on motor function remains to be seen, al-

though a mood-enhancing effect of rasagiline could potentially account for this discrepancy.

This, randomized-start, double-blind clinical trial is unique in demonstrating improvement of QOL compared to placebo by an anti-parkinsonian drug in early PD. Further studies may be necessary to determine the impact of rasagiline on QOL in combination with dopaminergic therapy, to determine whether rasagiline exerts its effects on QOL through antidepressant activity and whether treatment with rasagiline has long-term effects on QOL.

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APPENDIX

The following members of the Parkinson Study Group participated in this study and contributed toward this report:

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