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Rasagiline monotherapy in early Parkinson's disease: A phase 3, randomized study in Japan

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ABSTRACT

Background: Rasagiline is a monoamine oxidase type-B inhibitor in development in Japan for Parkinson's disease (PD). The objective of this Phase 3, randomized, double-blind study was to evaluate the efficacy and safety of rasagiline in Japanese patients with early PD (NCT02337725).

Methods: Patients were 30–79 years old with a diagnosis of PD within 5 years. Following a two-week placebo run-in period, patients were randomized 1:1 to receive rasagiline (1 mg/day) or placebo for up to 26 weeks. The primary endpoint was change from baseline in the MDS-UPDRS Part II + III total score (TS). Secondary endpoints included the MDS-UPDRS Parts II + III, III, II, and I TS and safety.

Results: In total, 118 patients were randomized to rasagiline and 126 to placebo. Patient characteristics at baseline were similar in both groups. The change from baseline in the MDS-UPDRS Part II + III TS was significantly greater in the rasagiline vs. placebo group (rasagiline-placebo: −6.39, 95% CI: −8.530, −4.250; $P < 0.0001$). The mean changes from baseline in the MDS-UPDRS Part II + III, Part III and Part II TS were lower at treatment visits between weeks 6 and 26 in the rasagiline vs. placebo groups. The overall incidence of treatment-emergent adverse events (TEAEs) was 62.4% and 52.4% in the rasagiline and placebo groups, respectively; most frequent TEAE was nasopharyngitis (15.4% and 15.1%).

Conclusion: Treatment with oral rasagiline 1 mg/day was effective and well-tolerated in Japanese patients with early PD, with a significantly greater improvement in the MDS-UPDRS Part II + III TS vs. placebo, and a similar safety profile.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease [1,2], affecting more than 1% of people aged older than 60 years old, and up to 4% of those aged more than 80 years old, worldwide [3]. In Japan, the overall prevalence is estimated to be between 100 and 150 per 100,000 people [4].

Loss of dopaminergic neurons and resulting deficiency in dopaminergic neurotransmission in the nigrostriatal pathway underlies the classical parkinsonian motor symptoms: bradykinesia, resting tremor, muscle rigidity, and postural instability [1,4]. There is no cure for PD, but current treatment options to alleviate symptoms include levodopa, dopamine agonists, and monoamine oxidase B inhibitors (MAOB-Is) [1,3–5]. MAOB-Is act by inhibiting the breakdown of dopamine by monoamine oxidase, thereby increasing the amount of dopamine in the striatum [6]. Levodopa is a precursor of dopamine and is the most effective and commonly used drug for the symptomatic treatment of PD, but long-term use is associated with motor complications [1,3–5,7]. Consequently, MAOB-Is have been recommended as first-line treatment for mild PD in Western countries [3,5]. In Japan, treatment and management guidelines for PD published by the Japanese Society of Neurology in 2011, recommend that treatment of symptoms should begin with levodopa or a dopamine agonist [8], because monotherapy using selegiline (the only MAOB-I available in Japan when the guidelines were published) was not approved until 2015 [9].

Rasagiline is a selective and irreversible MAOB-I [7], which has

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been evaluated in four key Phase 3 clinical trials, in North America and Europe [10–13]. In the TEMPO study, patients with early PD who received 1 mg/day rasagiline monotherapy for 26 weeks had a 4.2-point reduction in Unified Parkinson's Disease Rating Scale (UPDRS) total score, greater than the reduction that occurred with placebo [11]. In the ADAGIO study, between weeks 12 and 36 of treatment, an increase in UPDRS score occurred in the placebo group, with a smaller increase in the rasagiline 1 mg/day group; early-treatment with 1 mg/day (but not 2 mg/day) rasagiline was superior to delayed-start treatment [10]. Quality of life measured using the Parkinson's Disease Quality of Life questionnaire (PDQUALIF) was shown to be improved after 26 weeks of rasagiline therapy [14]. The efficacy and safety of rasagiline as an adjunct to levodopa have also been demonstrated in patients with more advanced disease [12,13]. As of June 2017, rasagiline is approved in 55 countries, including the USA and several European countries, for treatment of PD as monotherapy or combination therapy with levodopa or a dopamine agonist [15].

To date, no controlled studies have evaluated rasagiline monotherapy for Japanese patients with early PD. We conducted a study to evaluate the efficacy and safety of 26 weeks of oral rasagiline (1 mg/day) as monotherapy in Japanese patients with early PD, using changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale scores [16,17] (MDS-UPDRS) as efficacy endpoints.

2. Methods

2.1. Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study (NCT02337725) to evaluate the efficacy and safety of rasagiline in Japanese patients with early PD. The study consisted of an initial two-week single-blind run-in period, in which patients received placebo once daily for 2 weeks, followed by a 26-week double-blind treatment period, in which patients were randomized 1:1 to receive either placebo or oral rasagiline 1 mg/day (Supplementary Fig. 1).

The run-in period was designed to reduce the influence of placebo response on the study results.

The study was reviewed and approved by the Institutional Review Board (IRB) at each of the participating study centers.

2.2. Patients

Eligible patients were aged 30–79; had been diagnosed with PD in the previous 5 years; had at least two of the following symptoms: resting tremor, akinesia/bradykinesia, muscle rigidity; had a MDS-UPDRS Part II + Part III total score ≥14, and a modified Hoehn & Yahr [18] stage score of 1–3 at the start of the run-in period (visit 1). For enrollment into the treatment period, patients were required to have a MDS-UPDRS Part II + Part III total score of ≥14 at baseline (week 0).

Key exclusion criteria included: use of any investigational drug within 90 days prior to visit 1; previous use of rasagiline; a Mini-Mental State Examination (MMSE) score ≤24; treatment with amantadine or an anticholinergic drug for ≥180 days; treatment with selegiline, levodopa or dopamine agonists for ≥90 days; use of selegiline within 90 days of visit 1, or of any medication containing levodopa, dopamine agonists, amantadine or anticholinergic drugs within 30 days of visit 1. Concomitant use of antidepressants was prohibited.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as well as Good Clinical Practice, and all applicable laws and regulations. All patients provided written, informed consent.

2.3. Endpoints and assessments

The primary endpoint was the change in MDS-UPDRS Part II (motor aspects of activities of daily living) + Part III (motor examination) total score from baseline (week 0) to week 26 (Last Observation Carried Forward [LOCF]) of the treatment period. The secondary endpoints were changes from baseline to each visit throughout the treatment period in: MDS-UPDRS Part II + Part III total score; MDS-UPDRS Part I (non-motor aspects of experiences of daily living) total score; MDS-UPDRS Part II total score; and MDS-UPDRS Part III total score. Additional endpoints were proportion of patients with a change from baseline to week 26 in the MDS-UPDRS Part II + Part III total score < 3, changes from baseline to week 26 (LOCF) in MDS-UPDRS tremor, bradykinesia, and muscle rigidity scores, and in the Parkinson's Disease Questionnaire-39 (PDQ-39) [19] summary index and scores for individual domains of the PDQ-39. Safety was assessed by evaluating the incidence of treatment-emergent adverse events (TEAEs), classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

The MDS-UPDRS evaluation was performed by accredited investigators (except Part IB and Part II, which were self-evaluated by patients). Scores were recorded at every visit, except week 3. The PDQ-39 questionnaire was self-administered and scores were recorded at weeks 0, 14 and 26.

2.4. Statistical analysis

An analysis of covariance (ANCOVA) model was used to evaluate the least square (LS) mean change in the MDS-UPDRS scores from baseline to week 26 for the primary endpoint, and from baseline to each visit of the treatment period for the secondary endpoints, with baseline values as covariates. Logistic regression was performed to evaluate the odds ratio for a change from baseline to week 26 in the MDS-UPDRS Part II + Part III total score being < 3. Changes in PDQ-39 scores from baseline to week 26 were also analyzed by ANCOVA. Missing data were accounted for by the LOCF method.

For sample size calculation, a two-sample *t*-test with a two-sided 5% significance was applied. Assuming the effect size for the mean difference in the change from baseline to week 26 in MDS-UPDRS Part II + Part III total scores between the rasagiline and placebo groups to be −0.44, a sample size of 240 patients (120 per group) was found to provide 90% power to detect a statistically significant difference between treatment groups.

3. Results

3.1. Patients

The study was conducted at 68 sites in Japan, between February 2015 and September 2016. Of the 267 screened patients, 253 were enrolled into the run-in period. Of these, 244 were randomized to receive placebo (n = 126) or rasagiline (n = 118); 100 patients in the placebo group and 110 patients in the rasagiline group completed the study (Supplementary Fig. 2). The main reason for discontinuation in the placebo and rasagiline groups was voluntary withdrawal and adverse events, respectively.

At baseline (week 0), patient characteristics were generally well balanced between treatment groups (Table 1). The mean MDS-UPDRS Part II + Part III total score was 33.8 in the placebo group and 34.4 in the rasagiline group.

3.2. Efficacy

At week 26 (LOCF), the LS mean change from baseline in the MDS-UPDRS Part II + Part III total score (primary endpoint) was 1.87 (95% confidence interval [CI]: 0.385, 3.347) for the placebo group and −4.52 (95% CI: −6.068 -2.980) for the rasagiline group (Table 2), representing a relative improvement in symptoms for patients receiving rasagiline vs. placebo. The difference between groups was statistically

Table 1
Patients' baseline demographics and clinical information.

	Placebo n = 126	Rasagiline n = 118
Age, years, mean (SD)	65.4 (8.81)	67.4 (8.96)
≥65 years, n (%)	79 (62.7)	79 (66.9)
Female, n (%)	72 (57.1)	65 (55.1)
Duration of Parkinson's disease, years; mean (SD)	1.56 (1.24)	1.97 (1.97)
Modified Hoehn & Yahr stage, mean (SD)	2.15 (0.62)	2.18 (0.63)
MDS-UPDRS Part II + Part III total score, mean (SD)[a]	33.8 (14.43)	34.4 (16.95)
MDS-UPDRS Part I total score, mean (SD)[a]	5.7 (3.58)	5.5 (3.83)
MDS-UPDRS Part II total score, mean (SD)[a]	7.0 (4.64)	7.2 (5.47)
MDS-UPDRS Part III total score, mean (SD)[a]	26.8 (11.59)	27.2 (13.80)
MDS-UPDRS tremor score, mean (SD)[a]	5.8 (4.64)	5.7 (4.52)
MDS-UPDRS bradykinesia score, mean (SD)[a]	11.6 (5.92)	12.3 (7.06)
MDS-UPDRS rigidity score, mean (SD)[a]	6.2 (3.33)	5.9 (3.34)
PDQ-39 summary index, mean (SD)[a]	11.98 (11.52)	10.50 (10.04)
Levodopa use before the start of the study, n (%)[b]	16 (12.70)	15 (12.82)
Dopamine agonist before the start of the study, n (%)[b]	1 (0.79)	1 (0.85)

The data shown are for all randomized patients, unless specified.
SD: standard deviation; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39: Parkinson's Disease Questionnaire-39.
[a] At the end of the run-in period.
[b] 31–90 days before the run-in period; safety analysis set (placebo, n = 126; rasagiline, n = 117).

significant (rasagiline-placebo: −6.39, 95% CI: −8.530, −4.250; P < 0.0001).

There was a greater decrease in the MDS-UPDRS Part II + Part III and Part III total scores from baseline at treatment visits between weeks 6 and 26 (inclusive) in the rasagiline group compared with the placebo group (Fig. 1A, B). Between weeks 6 and 26, the MDS-UPDRS Part II score increased with placebo, but not with rasagiline, representing an improvement in symptoms in the rasagiline group compared with placebo (Fig. 1C). For the MDS-UPDRS Part I total score, the mean change from baseline was similar for both groups at week 6, but was less for the rasagiline group than the placebo group between weeks 10 and 26 (Fig. 1D).

The LS mean change from baseline to week 26 (LOCF) in the MDS-UPDRS Part III total score was −0.48 and −4.47 for the placebo and rasagiline groups, respectively; the between-group difference was statistically significant (−3.98, 95% CI: −5.800, −2.165; P < 0.0001). There was an increase in MDS-UPDRS Part II and Part I total scores from baseline to week 26 (LOCF) in both treatment groups; it was greater in the placebo group. The LS mean difference between groups was statistically significant for both Part II (−2.19, 95% CI: −3.143, −1.235, P < 0.0001) and Part I total scores (−0.80, 95% CI: −1.504, −0.099, P = 0.0255) (Table 2).

The proportions of patients with a change from baseline to week 26 in the MDS-UPDRS Part II + Part III total score of < 3 were 81.7% and 53.6% in the rasagiline and placebo groups, respectively; this difference was statistically significant (odds ratio 3.93; 95% CI: 2.172, 7.123; P < 0.0001). LS mean changes from baseline to week 26 (LOCF) with placebo and rasagiline were 0.02 and −1.20, respectively, for MDS-UPDRS tremor, −0.14 and −1.69 for MDS-UPDRS bradykinesia, and −0.21 and −1.00 for MDS-UPDRS rigidity (Table 2). All the differences between treatment groups were statistically significant.

At week 26 (LOCF), the LS mean change from baseline in the PDQ-39 summary index was 2.84 for the placebo group vs. 1.24 for the rasagiline group; the difference between groups was not statistically

Table 2
Changes in MDS-UPDRS scores between baseline and week 26 (LOCF).

	LS mean (SE)	Two-sided 95% CI	Difference between treatment groups (rasagiline-placebo)	Two-sided 95% CI	*P* value
MDS-UPDRS Part II + Part III					
Placebo	1.87 (0.752)	0.385, 3.347	–	–	–
Rasagiline	−4.52 (0.784)	−6.068, −2.980	−6.39	−8.530, −4.250	< 0.0001
MDS-UPDRS Part III					
Placebo	−0.48 (0.639)	−1.741, 0.775	–	–	–
Rasagiline	−4.47 (0.666)	−5.777, −3.154	−3.98	−5.800, −2.165	< 0.0001
MDS-UPDRS Part II					
Placebo	2.32 (0.335)	1.661, 2.983	–	–	–
Rasagiline	0.13 (0.350)	−0.555, 0.822	−2.19	−3.143, −1.235	< 0.0001
MDS-UPDRS Part I					
Placebo	0.98 (0.247)	0.496, 1.470	–	–	–
Rasagiline	0.18 (0.257)	−0.324, 0.687	−0.80	−1.504, −0.099	0.0255
MDS-UPDRS tremor score					
Placebo	0.02 (0.223)	−0.425, 0.455	–	–	–
Rasagiline	−1.20 (0.232)	−1.654, −0.741	−1.21	−1.846, −0.578	0.0002
MDS-UPDRS bradykinesia score					
Placebo	−0.14 (0.344)	−0.819, 0.535	–	–	–
Rasagiline	−1.69 (0.358)	−2.395, −0.983	−1.55	−2.525, −0.569	0.0021
MDS-UPDRS rigidity score					
Placebo	−0.21 (0.166)	−0.534, 0.121	–	–	–
Rasagiline	−1.00 (0.173)	−1.343, −0.660	−0.80	−1.269, −0.322	0.0011

MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; LOCF: Last Observation Carried Forward; LS: least squares; SE: standard error; CI: confidence interval.

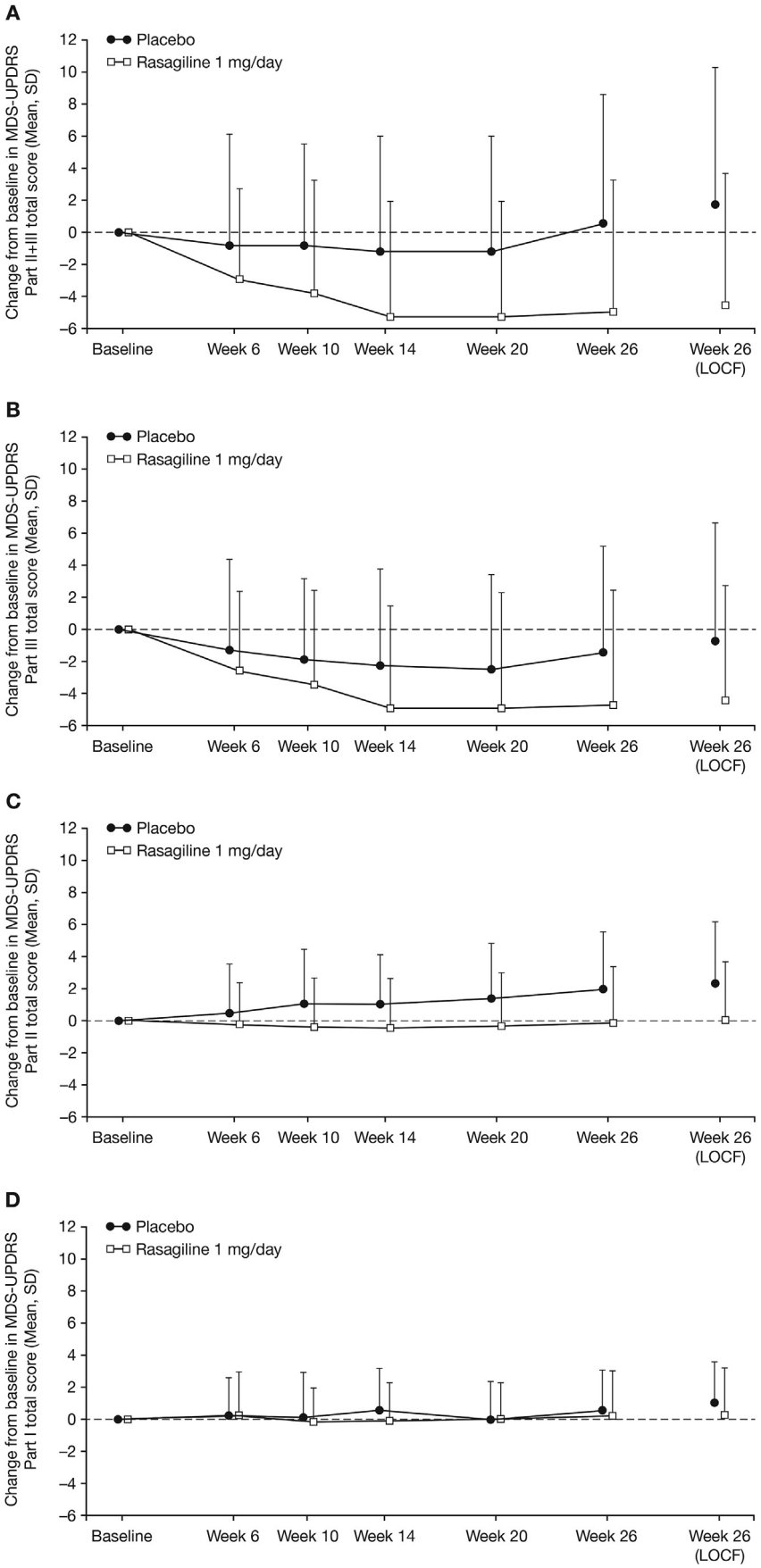

Fig. 1. MDS-UPDRS Part II + Part III (A), Part III (B), Part II (C) and Part I (D) total scores change from baseline over time (Abbreviation: SD: standard deviation; LOCF: Last Observation Carried Forward; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale).

Table 3
Changes in PDQ-39 scores between baseline and week 26 (LOCF).

	Placebo LS mean (SE)	Rasagiline	Difference between treatment groups (rasagiline-placebo)	Two-sided 95% CI	*P* value
PDQ-39 summary index	2.84 (0.699)	1.24 (0.723)	−1.60	−3.586, 0.381	0.1128
Domain scores					
Mobility	4.05 (1.182)	1.64 (1.222)	−2.41	−5.763, 0.936	0.1571
Activities of daily living	5.66 (1.155)	0.98 (1.195)	−4.68	−7.950, −1.401	0.0053
Emotional well-being	3.59 (1.044)	−0.11 (1.080)	−3.70	−6.669, −0.724	0.0150
Stigma	1.21 (0.980)	0.06 (1.014)	−1.16	−3.946, 1.633	0.4149
Social support	2.01 (0.769)	1.11 (0.795)	−0.90	−3.075, 1.282	0.4184
Cognition	2.47 (0.900)	2.14 (0.931)	−0.33	−2.884, 2.222	0.7987
Communication	1.92 (0.992)	0.77 (1.026)	−1.15	−3.963, 1.667	0.4225
Bodily discomfort	2.75 (1.345)	2.28 (1.391)	−0.47	−4.284, 3.348	0.8093

PDQ-39: Parkinson's Disease Questionnaire-39; LOCF: Last Observation Carried Forward; LS: least squares; SE: standard error; CI: confidence interval.

significant (−1.60, 95% CI: −3.586, 0.381, P = 0.1128) (Table 3). Mean changes from baseline for all individual domain scores were numerically greater for the rasagiline group than the placebo group; the differences between groups were statistically significant for the domains *activities of daily living* (rasagiline-placebo: −4.68, 95% CI: −7.950, −1.401, P = 0.0053) and *emotional well-being* (rasagiline-placebo: −3.70, 95% CI: −6.669, −0.724, P = 0.0150).

3.3. Safety

The proportion of patients who completed 24 weeks or more of treatment was 79.4% in the placebo group and 93.2% in the rasagiline group. Treatment duration was on average 157.4 (± 49.3) and 173.5 (± 31.7) days for the placebo and rasagiline groups, respectively.

The overall incidence of TEAEs was lower for the placebo group (52.4% [66/126]) than the rasagiline group (62.4% [73/117]). Most TEAEs in either treatment group were mild or moderate in severity; 35 patients in the placebo group (27.8%) had drug-related TEAEs, compared with 46 in the rasagiline group (39.3%). TEAEs leading to discontinuation occurred in 8 patients in the placebo group (6.3%) and 3 patients in the rasagiline group (2.6%) (Supplementary Table 1). The most frequent TEAE was nasopharyngitis, occurring in approximately 15% of patients in both treatment groups (Supplementary Table 2). TEAEs related to study-drug with an incidence ≥3% in either group were nasopharyngitis, (2.4%/4.3%, placebo/rasagiline) and eczema (1.6%/4.3%). Serious TEAEs occurred in 8 patients in the placebo group (6.3%) and in 4 patients in the rasagiline group (3.4%). Drug-related serious TEAEs occurred in 5 (4.0%) and zero patients in the placebo and rasagiline groups, respectively, while 4 (3.2%) and 1 (0.9%), respectively, discontinued from the study due to serious TEAEs. There was one death during the study in the placebo group; the cause of death was completed suicide; this was judged to be unlikely to be related to the study drug.

4. Discussion

To our knowledge, this was the first large randomized clinical trial in patients with PD in Japan to utilize changes in MDS-UPDRS scores as efficacy endpoints (instead of UPDRS scores). Although UPDRS is a commonly used and validated scale for assessment of efficacy of PD symptoms [20], the MDS-UPDRS is an updated and improved scale, the results of which correlate with those of the original UPDRS, and have been validated for the assessment of PD symptoms [16]. One of the major changes in the revision of the UPDRS scale was the expansion of the non-motor part in the MDS-UPDRS scale [16]. A validated Japanese translation of the MDS-UPDRS was used in this study [17].

The primary endpoint was the change in the MDS-UPDRS Part II + Part III total score from baseline to week 26 (LOCF). An improvement of −4.52 was observed in rasagiline-treated patients, compared with a worsening of 1.87 in placebo-treated patients, the difference between treatments was statistically significant.

The most notable improvement with rasagiline therapy in any individual domain was with regard to the motor examination subscale (MDS-UPDRS Part III total score), with a −4.47 point difference to the baseline score, which, according to Horvath et al. is clinically meaningful [21]. These authors found a change of −3.25 in MDS-UPDRS Part III total score to be the minimal clinically meaningful improvement [21]. For MDS-UPDRS Part II total score, changes of −3.05 and 2.51 were considered to be clinically meaningful improvement and worsening, respectively [22]. In the present study, changes from baseline to week 26 (LOCF) of 0.13 and 2.32 in MDS-UPDRS Part II total score were observed for rasagiline and placebo, respectively. Therefore, the change in the rasagiline group was not clinically meaningful, while an almost clinically meaningful worsening was observed in the placebo group. The changes from baseline in MDS-UPDRS Part II + Part III, Part III, and Part II total scores at weeks 6, 10, 14, and 20 also indicated a relative improvement with rasagiline therapy; the differences in favor of rasagiline were maintained from week 6 until the end of the study.

In the TEMPO study in North-American patients with early PD receiving rasagiline 1 mg/day as first-line treatment, there was a difference of −4.2 in the UPDRS total score, and of −2.7 in the UPDRS Part III score, compared with placebo [11]. A meta-analysis of randomized clinical trials in patients with early PD identified a reduction in UPDRS total score of approximately 3 points between rasagiline and placebo [23]. Another meta-analysis of 12 randomized trials of MAOB-Is (mostly selegiline) in patients with early PD receiving first-line therapy or starting treatment in the previous 12 months demonstrated a similar benefit of −3.8 in the UPDRS motor score [24]. Most recently, an improvement of −3.01 in the UPDRS Part II + Part III total score was reported after 12 weeks treatment with selegiline in Japanese patients [25]. Although the UPDRS scale was used, the symptomatic benefit provided by rasagiline in the above studies can be considered similar to the present study in Japanese patients, in which the MDS-UPDRS scale was used.

Regarding the MDS-UPDRS Part I total score, in the present study the rasagiline-placebo difference in the change from baseline to week 26 was statistically significant at −0.80. This was similar to the finding observed in the ADAGIO study, in which a draft version of the MDS-UPDRS Part I total was used in a secondary analysis: the change from baseline to week 36 was 0.34 in the placebo group, and 0.01 in the rasagiline 1 mg/day group, with a −0.33 between-group difference [26].

The change in the PDQ-39 questionnaire summary index score after 26 weeks of treatment was numerically greater in the rasagiline group compared with placebo in the present study, but the difference was not statistically significant. Because the present study was not powered to detect changes in this measure, a potential reason for this lack of significance is the relatively low PDQ-39 summary index score observed for both treatment groups at baseline, which implies that a greater number of patients would have been required to detect a significant difference. Furthermore, the relative insensitivity to change of this measure in patients with early PD has been previously suggested in

entacapone studies [27,28]. Nevertheless, for the activities of daily living and emotional well-being sub-scores, a statistically significant difference in the change from baseline was observed in rasagiline patients compared with placebo. Patient-reported outcomes in previous trials have also shown to be improved following rasagiline therapy. For example, in the TEMPO trial there were improvements from baseline to week 26 in the PDQUALIF scale score with rasagiline 1 mg/day and 2 mg/day, but not with placebo [11,14]. In the PRESTO trial, a trend towards improvement in the PDQUALIF scale score was demonstrated for 0.5 mg/day rasagiline, but not with 1 mg/day rasagiline [12].

In terms of safety, the majority of TEAEs reported during treatment with rasagiline in this study were mild, and no new safety concerns were identified. There was a higher incidence of TEAEs in the rasagiline group (62.4% vs. 52.4%), including those deemed to be related to the study drug (39.3% vs. 27.8%), than in the placebo group. Serious TEAEs, however, occurred in more patients receiving placebo (6.3%) than in those receiving rasagiline (3.4%). Only two TEAEs had an incidence of ≥5%, namely nasopharyngitis and fall, and at similar rates between treatment groups. In the TEMPO trial, TEAEs occurred at similar rates in the rasagiline and placebo groups, the overall incidence (approximately 80%) being somewhat higher than in the current study [11].

A potential limitation of the present study is that it was not designed to detect the onset time of efficacy with rasagiline treatment, as the first assessment was performed after 6 weeks of treatment, and it is possible that efficacy could have been observed before that time. In addition, given the chronic nature of the disease, the study was performed for a relatively short duration of time; further studies are warranted to evaluate the long-term efficacy of rasagiline in Japanese patients.

In conclusion, this Phase 3 study provides evidence that oral rasagiline 1 mg/day is effective at improving symptoms of PD, including motor symptoms, and is well tolerated in Japanese patients with early disease. Subject to receiving official approval, rasagiline represents a potentially valuable new treatment option as monotherapy for Japanese patients with early PD.

Conflicts of interest

Nobutaka Hattori has served on advisory boards for Hisamitsu Pharmaceutical Co., Inc., Sumitomo Dainippon Pharma Co. Ltd, Ono Pharmaceutical Co. Ltd, Otsuka Pharmaceutical, Co. Ltd, Novartis Pharma K.K., and Takeda Pharmaceuticals Co. Ltd; has performed corporate-sponsored research for Takeda Pharmaceutical Co. Ltd; has received honoraria from GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co. Ltd, FP Pharmaceutical Corporation, Sumitomo Dainippon Pharma Co. Ltd, Eisai Co. Ltd, Kissei Pharmaceutical Company, Nihon Medi-physics Co. Ltd, Kyowa Hakko-Kirin Co. Ltd, Novartis Pharma K.K., Biogen Japan Ltd, Acorda Therapeutics Inc., Otsuka Pharmaceutical Co. Ltd, Janssen Pharmaceutical K.K., Medtronic Japan Co. Ltd, Astellas Pharma Inc.; has received donations from Astellas Pharma Inc., Eisai Co. Ltd, MSD K.K., Daiichi Sankyo Co. Ltd, Novartis Pharma K.K., Takeda Pharmaceutical Co. Ltd, Nihon Medi-physics Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Pfizer Japan Inc., Bayer Yakuhin Ltd, FP Pharmaceutical Corporation, Shionogi & Co. Ltd, MSD; and has received donations for the endowed research departments GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Eisai Co. Ltd, Kissei Pharmaceutical Co., Nihon Medi-physics Co. Ltd, Kyowa Hakko-Kirin Co. Ltd, Medtronic Japan Co. Ltd, Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Zaiho Co., Asahi Kasei Medical Co. Ltd, MiZ Co. Ltd. Atsushi Takeda has served on advisory boards for AbbVie Inc., Kyowa Hakko Kirin Co. Ltd, and Takeda Pharmaceutical Co. Ltd; has performed corporate-sponsored research for Hisamitsu Pharma Co. Inc., Meiji-Seika Pharma Co. Ltd, Pfizer Japan Inc.; and has received honoraria from AbbVie Inc., Sumitomo Dainippon Pharma Co. Ltd, Kyowa Hakko Kirin Co. Ltd. Shinichi Takeda, Akira Nishimura, and Tadayuki Kitagawa are employees of Takeda Pharmaceutical Co. Ltd. Hideki Mochizuki has served on advisory boards for Hisamitsu Pharmaceutical Co. Inc., Takeda Pharmaceutical Co. Ltd; has received honoraria from FP Pharmaceutical Corporation, Sumitomo Dainippon Pharma Co. Ltd, Nihon Medi-physics Co. Ltd, Kyowa Hakko-Kirin Co. Ltd, Novartis Pharma K.K., Otsuka Pharmaceutical Co. Ltd; has received donations from, Nihon Medi-physics Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Kyowa Hakko-Kirin Co. Ltd. Masahiro Nagai has served on an advisory board for Takeda Pharmaceuticals Co. Ltd; and has received honoraria from Novartis Pharma K.K. Ryosuke Takahashi is an employee of the Japan Agency for Medical Research and Development; has served on advisory boards for Kan Research Institute Inc. and Sumitomo Dainippon Pharma Co. Ltd; has performed corporate-sponsored research for Novartis Pharma K.K. Co., Otsuka Pharmaceutical Co. Ltd, Pfizer Japan Inc., Takeda Pharmaceuticals Co. Ltd, Nippon Boehringer Ingelheim Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Kyowa Hakko Kirin Co. Ltd, Nihon Medi-Physics Co. Ltd, Mitsubishi Tanabe Pharma Co. and Konica Minolta Inc.; and has received honoraria from Sumitomo Dainippon Pharma Co Ltd and FP Pharmaceutical Co.

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The sponsor was involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.08.024.

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