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Original article

Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease

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Abstract

Objective:
Rasagiline is a second-generation, irreversible MAO-B inhibitor (MAOB-I) previously shown to be efficacious and well-tolerated compared to placebo in the treatment of early Parkinson's disease (PD). ACTOR (**AC**ceptabilité **TO**lérance **R**asagiline) was a 15-week, multi-center, randomized, double-blind study aimed to assess the safety and tolerability of rasagiline compared to the dopaminergic agonist pramipexole in the treatment of early PD.

Methods:
Patients with early, untreated idiopathic PD were randomized to receive 1 mg rasagiline ($n = 53$) or 1.5 mg pramipexole ($n = 56$) daily. The primary outcome was the number of patients experiencing a 'clinically important adverse event' (classified as a serious adverse event, an event leading to withdrawal or severe according to the patient). Safety outcomes were evaluated by the investigator and the patient. Analysis of the primary criterion was a comparative analysis using the chi-squared test. The Wilcoxon Mann–Whitney test was conducted to test the severity of patient-reported adverse events. Other tests performed include a covariance analysis and Student's *t*-tests.

Results:
Mean disease duration was 3.4 months, and mean age was 62.6 years. Of patients taking pramipexole, 44.6% reported at least one 'clinically important' adverse event compared to 32.1% of patients taking rasagiline; non-inferiority of rasagiline was reached, with a difference in proportions of −12.6% [confidence interval of −27.8%; 2.6%]. There were no significant differences in clinical effectiveness between the treatments, measured by clinical and patient global impression of improvement (CGI-I, PGI-I) and PDQ-8 scales. A significant decrease in the incidence of gastrointestinal symptoms ($p = 0.015$) and sleep disorders ($p = 0.027$) was reported by physicians in the rasagiline group compared to the pramipexole group; the propensity to sleepiness improved significantly in the rasagiline group ($p = 0.020$), and worsened in the pramipexole group ($p = 0.042$).

Limitations:
Limitations of this study include the limited sample size due to the lower than anticipated recruitment and the accidental inclusion of a patient who had taken contraindicated medication.

Conclusions:
In this study, the safety profile of rasagiline had clinically favorable differences in gastrointestinal and sleep adverse events compared to pramipexole, whilst showing comparable clinician and patient-rated clinical effectiveness as a monotherapy for the treatment of early idiopathic PD.

Introduction

Rasagiline is a second-generation, potent, irreversible MAOB-I which has previously been demonstrated to be efficacious and well-tolerated, compared to placebo, in early Parkinson's disease (PD)[1,2]. Rasagiline has also been shown to significantly delay the need for additional symptomatic antiparkinsonian drugs in previous clinical trials[3], with 46% of patients remaining on rasagiline monotherapy after 2 years[4]. Pramipexole is a dopaminergic agonist, which has also been demonstrated to be effective compared to placebo and levodopa in previous randomized controlled trials, with a lower incidence of dyskinesia and 'wearing-off' compared to levodopa[5].

Patient perception of the treatment regime in terms of balancing both effectiveness and tolerability is an important factor to consider when initiating treatment in early PD. Non-adherence is a frequent occurrence in clinical practice, often related to the patient's personal experiences, expectations and beliefs about a treatment[6–8]. Varying adherence and persistence has been demonstrated across different PD therapies, with the adherence rate for rasagiline found to be significantly higher than for other drugs[8]. Therefore, it is important to consider patient-reported effectiveness and adverse-event data, in order to assess whether the clinical outcomes reflect the views of the patients.

In a 15-week, comparative, randomized trial we aimed to evaluate the safety and tolerability of rasagiline compared to pramipexole as a monotherapy in the treatment of idiopathic early PD, and the 'clinical usefulness' of rasagiline and pramipexole, including both clinician and patient perceptions of the treatment regimen in terms of effectiveness and acceptability.

Patients and methods

Trial design

ACTOR (**AC**ceptabilité **TO**lérance **R**asagiline) was a phase IV, multicenter, comparative, randomized, parallel-group, double-blind trial with a total duration of 15 weeks. Patients between the ages of 18 and 70 years with idiopathic PD, diagnosed using conventional criteria, with a Hoehn and Yahr score $\leq$3 were recruited between December 2008 and March 2010 by 29 neurologists in France. Patients were randomized in a 1:1 ratio to receive 1 mg rasagiline once daily (plus placebo twice daily) or pramipexole three times daily, titrated from 0.375 mg/day in week 1, 0.75 mg/day in week 2 to a maximum dose of 1.5 mg/day in week 3 in accordance with the recommended daily dose.

To be included in the trial, patients must have never received anti-Parkinson treatment or had received levodopa for less than 12 weeks at a dose less than 200 mg; patients discontinued all anti-Parkinson treatment other than the study drugs as part of the study protocol. Twenty patients who had been treated with a dopaminergic agonist other than pramipexole were also included, on the condition that the patient was still in the titration phase at the time of inclusion, or that treatment was given for less than 6 weeks and had not been given for 2 weeks before the time of inclusion.

Exclusion criteria included pregnant or breastfeeding women, or women of a childbearing age without sterilization or a reliable birth control method; patients with liver disease; patients with a concomitant disease considered to be significant by the investigator; patients treated with cerebral stimulation and patients with skin lesions not assessed by a dermatologist. Patients treated with fluoxetine during the 5 weeks preceding inclusion, those treated with fluvoxamine, pethidine, selegiline or any other MAOB-I during the 2 weeks preceding inclusion and patients likely to receive dextromethorphan or a sympathomimetic drug during the trial were also excluded.

The protocol was approved by the local ethics committee and regulatory authority (Agence Française de Sécurité Sanitaire des Produits de Santé). The trial was conducted in accordance with the Declaration of Helsinki, and all patients gave written informed consent before participation.

Assessments

The primary outcome of the trial was the frequency of clinically important adverse events up to week 15, defined as the patient satisfying one or more of the following criteria; a serious adverse event (SAE), adverse events requiring a decision by the investigator of therapy or dose reduction, an adverse event considered moderate or severe by the patient (AEs whose intensity has not been assessed are considered moderate to severe). The criteria for clinically important adverse events were adapted from a previous study assessing tolerability of analgesics[9].

Serious adverse events were defined as cases causing patient death, hospitalization or prolongation of hospitalization, any adverse event leading to significant incapacity or disability, or cancer, any event that could be considered life-threatening but which did not cause death or hospitalization or prolongation of hospitalization or any overdose (of trial or other treatment). At each visit the investigator collected information relating to adverse events, and each patient completed a self-assessment questionnaire, which included a checklist of symptoms, a specific questionnaire about the quality of sleep and space for any comments from the patient.

Secondary safety outcomes were the percentage of patients with sleep disorders and the Epworth Sleepiness

Scale (ESS), based on the patient's self-assessment of the likelihood of daytime drowsiness in common real-life situations.

Secondary effectiveness outcomes were assessed using the Clinical Global Impression of Improvement (CGI-I) scale and the Patient Global Impression of Improvement (PGI-I) scale at each visit. Quality of life outcomes were assessed using the PDQ-8 scale and utility values were assessed using the EQ-5D and EQ-VAS questionnaires.

Statistical analysis

The study was initially designed to test the superiority of rasagiline compared to pramipexole for the primary outcome. A sample size of 240 patients needed was based on the hypothesis that there would be a 15% difference in clinically important adverse events between groups, with a type 1 risk (α) of 5% and a type 2 risk (β) of 20%. However, due to a decreased number of recruited patients compared to the initial expected sample size the protocol was amended, after approval by the ethics committee, such that the primary outcome was tested for the non-inferiority of rasagiline compared to pramipexole. In the amended protocol, 112 subjects included were sufficient to reach a pre-defined non-inferiority boundary of 10%. If the non-inferiority of rasagiline on the primary endpoint was demonstrated, all primary and secondary outcomes would subsequently be tested for superiority as defined in the initial protocol.

The analyzed population was defined as the intention-to-treat (ITT) group, which consisted of all included patients who had given their informed consent, and for whom at least one item of post-inclusion safety data was available. The per-protocol population (PP) consisted of patients in the ITT group without any consultation under treatment classified as major protocol deviations. If the patient was classified as a major deviation from visit 2 (V2), they were entirely excluded from the PP analysis. Quantitative variables were described in terms of their mean, standard deviation, median, minimum and maximum. Qualitative variables were described in terms of numbers and the percentage of each condition.

Analysis of the primary criterion was a comparative analysis of the percentage of patients in the two treated groups suffering at least one clinically important adverse event using the chi-squared test. A descriptive analysis of adverse events was given for each group, and further statistical analysis was conducted using the chi-squared test; severity of patient-reported adverse events was evaluated using the Wilcoxon Mann–Whitney test.

Covariance analysis was performed on the secondary outcomes of ESS, CGI-I, PGI-I, PDQ-8, EQ-5D and EQ-VAS to assess the difference between the two treatment groups; Wilcoxon Mann–Whitney and Student *t*-tests were used to assess the intra-group changes.

Results

Patient characteristics

Of the 112 patients assessed for eligibility, 109 patients were randomized in a 1:1 ratio to receive rasagiline or pramipexole (Figure 1). In the rasagiline group only three patients (5.7%) discontinued due to an adverse event compared to eight patients (14.3%) in the pramipexole group. Of those that discontinued in the rasagiline group, symptoms included nausea, headache, dizziness, hives, and serotonin syndrome. For the pramipexole group, discontinuations were mainly due to malaise ($n=2$) and nausea ($n=2$), with other reasons being abdominal pain (due to ovarian cancer), fatigue, depression and visual hallucination.

Patients included in the trial had an average age of 62.6 years and were predominantly male (62.4%). The majority of the patients were diagnosed with PD with a Hoehn and Yahr score ≤ 2 (43% with score 1; 51% with score 2), and an average time since diagnosis of 3.4 months; 81.7% of patients had never received any prior anti-Parkinson treatment. The two treatment groups were similar at baseline with regard to demographic variables (Table 1), with the exception of pain/cramp, which was significantly higher in the pramipexole group ($p=0.027$).

The mean duration of exposure to treatment was 102.4 ± 16 days in the rasagiline group and 95.1 ± 29.4 days in the pramipexole group (p-value not significant).

Safety outcomes

Overall, of those patients taking pramipexole, 44.6% reported at least one 'clinically important adverse event' compared to 32.1% of patients taking rasagiline. The non-inferiority of rasagiline was reached, with a difference in proportions of −12.6% [confidence interval of −27.8%; 2.6%], which was significantly lower than the pre-defined non-inferiority boundary of 10%. This difference did not reach statistical significance in the superiority analysis.

SAEs were reported in one patient in each treatment group. One patient developed serotonin syndrome after co-administration of fluoxetine and rasagiline, for which concomitant use is not recommended[10], following accidental inclusion in the trial due to the patient not declaring concurrent medication. The patient also had alcohol-induced fibrosis of the liver. The second SAE was in a patient in the pramipexole group, who withdrew from the trial after diagnosis of ovarian cancer; this event was not considered to be linked to the treatment.

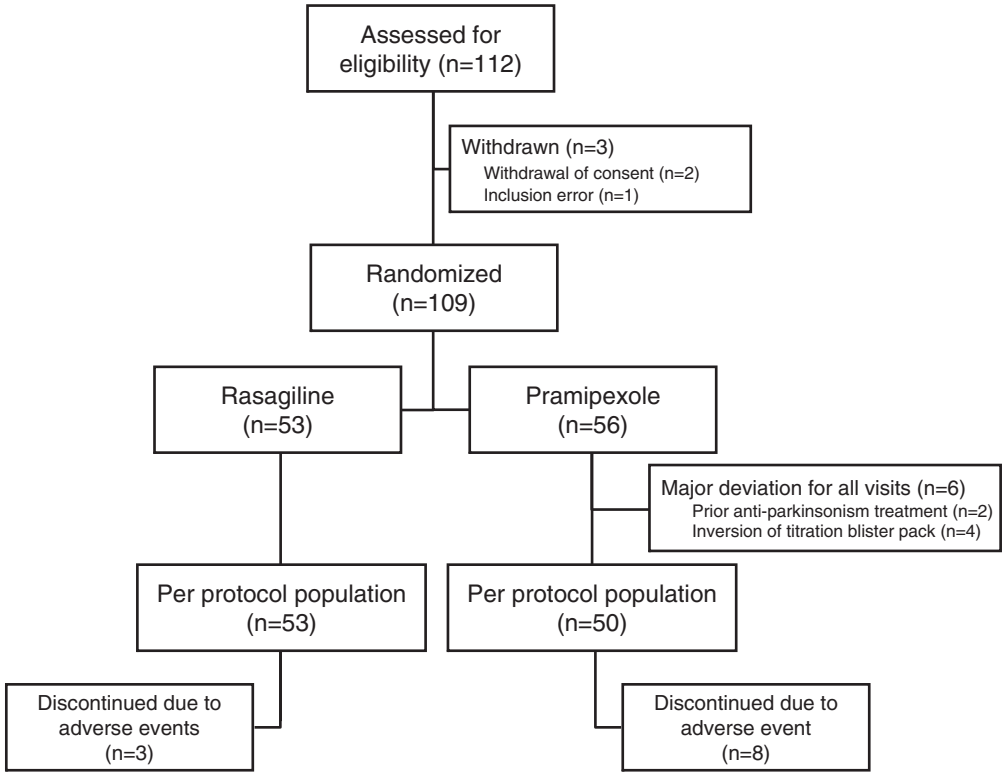

Figure 1. Patient disposition.

Table 1. Patient demographics, baseline characteristics and clinical form.

	Rasagiline group $n=53$	Pramipexole group $n=56$	*p*-values
Age (years)	63.2 ± 7.3	62.1 ± 6.2	NS
Age at onset of disease	62.2 ± 7.3	60.7 ± 6.1	NS
Female sex, *n* (%)	16 (30.2%)	25 (44.6%)	NS*
Time since diagnosis (months)	2.5 ± 3.8	4.3 ± 7.3	NS
Height (cm)	169.83 ± 9.36	166.80 ± 9.31	NS
BMI (kg/m^2)	25.98 ± 4.17	25.74 ± 4.02	NS
EQ-5D original score	0.75 ± 0.15	0.67 ± 0.25	NS
EQ-VAS score	67.48 ± 16.07	63.74 ± 18.76	NS
PDQ-8	5.45 ± 3.67	6.99 ± 5.23	NS
Epworth questionnaire (ESS)	6.42 ± 4.34	5.23 ± 3.93	NS
Previous anti-Parkinson treatment	11 (20.8%)	9 (16.1%)	NS*
History of depression	13 (24.5%)	20 (35.7%)	NS*
History of anxiety	26 (49.1%)	24 (42.9%)	NS*
Antidepressant in the previous 2 years	11 (20.8%)	15 (26.8%)	NS*
BZD in the previous 2 years	12 (22.6%)	10 (17.9%)	NS*
Clinical form			
Tremor	7 (13.2%)	13 (23.2%)	NS*
Mixed	34 (64.2%)	28 (50.0%)	NS*
Akinetic hypertonicity	12 (22.6%)	15 (26.8%)	NS*
Pain, cramp	28 (52.8%)	41 (73.2%)	0.027*
Sleep disorders	21 (39.6%)	21 (37.5%)	NS*
CGI			
Normal	1 (1.9%)	0	NS
Borderline	2 (3.8%)	1 (1.8%)	NS
Mild	34 (64.2%)	33 (58.9%)	NS
Moderate	12 (22.6%)	13 (23.2%)	NS
Obvious	4 (7.5%)	9 (16.1%)	NS

BZD, benzodiazepines; CGI, clinical global impression.
All values reported as mean ± SD or *n* (%) as appropriate.
All *p*-values calculated using Wilcoxon Mann–Whitney test except *chi-squared test.

Table 2. Adverse events reported by the physician in >5% of patients in either treatment group.

	Rasagiline ($n=53$)	Pramipexole ($n=56$)	p-values
Total patients with an AE as reported by the physician	36 (67.9%)	43 (76.8%)	NS*
Central nervous system	4 (7.5%)	6 (10.7%)	–
Malaise, syncope	2 (3.8%)	6 (10.7%)	NS
Nervous system	11 (20.8%)	13 (23.2%)	–
Headache	3 (5.7%)	5 (8.9%)	NS
Tingling	4 (7.5%)	2 (3.6%)	NS
Dizziness	3 (5.7%)	5 (8.9%)	NS
Gastrointestinal system	15 (28.3%)	27 (48.2%)	–
Gastralgia	4 (7.5%)	5 (8.9%)	NS
Constipation	2 (3.8%)	4 (7.1%)	NS
Nausea, vomiting	5 (9.4%)	16 (28.6%)	0.011*
Musculo-skeletal system	12 (22.6%)	14 (25.0%)	
Joint pain, joint disease	7 (13.2%)	12 (21.4%)	NS*
Muscle cramps	5 (9.4%)	2 (3.6%)	NS
Cardiovascular system	4 (7.5%)	6 (10.7%)	–
Orthostatic hypotension	1 (1.9%)	3 (5.4%)	NS
General disorders	11 (20.8%)	11 (19.6%)	–
Weight loss	3 (5.7%)	0	NS
Weight gain	2 (3.8%)	4 (7.1%)	NS
Weakness	6 (11.3%)	7 (12.5%)	NS*
Psychiatric disorders	18 (34.0%)	31 (55.4%)	–
Anxiety, irritability, emotionality	4 (7.5%)	4 (7.1%)	NS
Mood swings	5 (9.4%)	4 (7.1%)	NS
Hallucinations	0	3 (5.4%)	NS
Sleep disorder, daytime sleepiness	9 (17.0%)	20 (35.7%)	0.027*
Respiratory Tract	5 (9.4%)	5 (8.9%)	–
Respiratory infection	4 (7.5%)	5 (8.9%)	NS
Skin, hair and nails	8 (15.1%)	2 (3.6%)	–
Itching	3 (5.7%)	0	NS
Rash	5 (9.4%)	0	0.025

All values reported as n (%). Patients could report more than one type of AE.
All p-values calculated using Fisher's exact test except *chi-squared test.

Investigator-reported adverse events

At each visit, the investigator collected information regarding adverse events (AEs). AEs reported by the physician in more than 5% of patients in either treatment group are described in Table 2.

An adverse gastrointestinal event was reported in 12 patients in the rasagiline group (22.6%) compared to 25 patients in the pramipexole group (44.6%, $p=0.015$); the incidence of nausea and vomiting was notably higher in the pramipexole group compared to the rasagiline group (28.6 vs. 9.4%, $p=0.011$, Table 2). The incidence of rash was significantly higher in the rasagiline group compared to the pramipexole group (9.4 vs. 0%, $p=0.025$, Table 2).

At least one form of sleep disorder was reported in nine patients in the rasagiline group (17.0%) compared to 20 patients in the pramipexole group (35.7%, $p=0.027$). In the rasagiline group, the number of patients reporting at least one form of sleep disorder reduced from 21 patients (39.6%) at baseline to only nine patients (17%) during the trial; in the pramipexole group the incidence remained similar.

The propensity to sleepiness in both groups was monitored using the Epworth Sleepiness Scale, which was quoted by the investigator at each visit. There was a significant improvement in propensity to sleepiness in the rasagiline group over the entire trial period (mean change from baseline (SD), −0.88 (2.63), $p=0.020$) whereas pramipexole significantly worsened the propensity to sleepiness (1.04 (3.63), $p=0.042$). Overall, the two groups differed significantly in favor of rasagiline, as validated by covariance analysis ($p=0.007$).

Significantly more patients in the rasagiline group reported a weight gain of more than 5 kg over the trial period compared to the pramipexole group (15.4 vs. 3.6%, $p=0.048$). However, the number of patients who reported a clinically significant weight gain of more than 7% of their baseline body weight was comparable between the treatment groups.

Patient-reported adverse events

Alongside physician assessments, patients also completed a self-assessment questionnaire at each visit to record the presence and severity of adverse events in the previous weeks. Each symptom was considered to be absent if it was not declared during follow-up, and symptoms declared at least once were graded according to severity. If the event was declared multiple times, the severity level retained

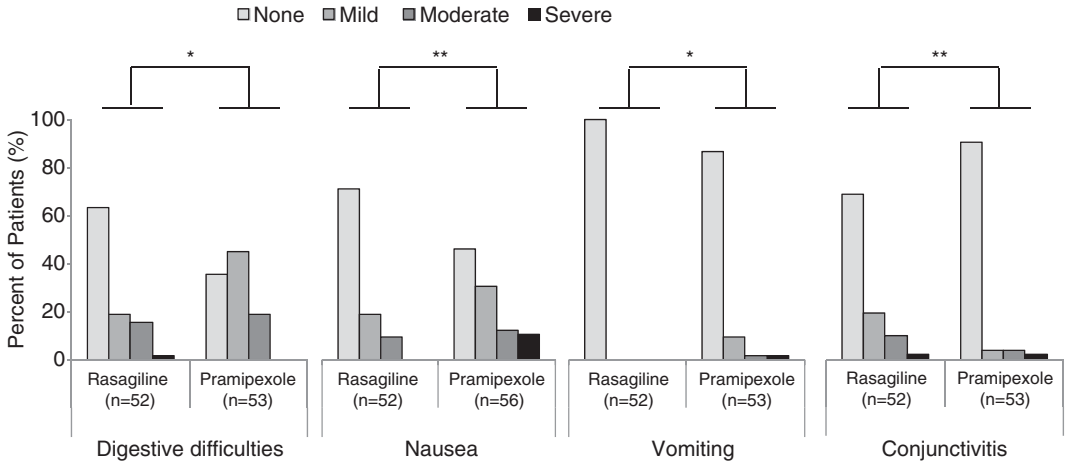

Figure 2. Frequency and severity of adverse events over 15 weeks in patients who completed the patient self-assessment questionnaire. *$p<0.05$, **$p<0.01$ (Wilcoxon Mann–Whitney).

was the highest level indicated. Digestive difficulties ($p=0.027$), nausea ($p=0.006$) and vomiting ($p=0.033$) were significantly less frequent overall in the rasagiline group compared to the pramipexole group (Figure 2). Red-eye conjunctivitis was significantly more frequent in the rasagiline group ($p=0.009$, Figure 2). All other symptoms were reported with a frequency and severity that was comparable between the two groups (data not shown).

Changes in behavioral symptoms linked to a lack of impulse control were also assessed using the self-assessment questionnaire completed by patients at each visit. There were no significant differences between the pramipexole and rasagiline groups in the number of patients reporting some behavior modifications, such as smoking more than usual (three patients (5.7%) vs. four patients (7.7%)), gambling more than usual (two patients (3.8%) vs. one patient (1.9%)) and spending more than usual (seven patients (13.2%) vs. four patients (7.7%)). Significantly more patients in the pramipexole group reported hypersexuality (nine patients (17%)) compared to the rasagiline group (two patients (3.8%), $p=0.028$).

Quality of life and efficacy outcomes

Quality of life (QoL) was assessed using the PDQ-8, EQ-5D and EQ-5D VAS scales. Mean scores for each measure over the course of the trial are shown in Figure 3. The changes in scores remained stable for all measures in the rasagiline group, and significantly improved from baseline to endpoint in the pramipexole group ($p<0.05$ for all scales). However, covariance analysis of EQ-5D and EQ-5D VAS did not reveal any significant differences in QoL outcomes between the two groups. Covariance analysis of the PDQ-8 scores was not valid due to an interaction between the covariant and the treatment.

At week 15, 71.2% of patients in the rasagiline group had a slight, significant, or very significant improvement on the CGI-I, compared to 65.5% of the pramipexole group (Figure 4). At the same time point, 67.3% of patients in the rasagiline group and 75.5% of patients in the pramipexole group reported a slight, significant, or very significant improvement on the PGI-I scale (Figure 4). There was no significant difference in symptom improvement between the two groups as measured by the Wilcoxon two-sample test.

Discussion

This phase IV, randomized, comparative, double-blind clinical trial indicates an improved safety profile of rasagiline, with significantly fewer gastrointestinal and sleep related events, whilst offering similar clinical effectiveness measured by the CGI-I, PGI-I and quality of life assessments. There were fewer clinically important adverse events with rasagiline compared to pramipexole, as reported by both the physician and the patient; the non-inferiority of rasagiline was demonstrated for this outcome. Patient assessment of adverse events also reflected the investigator reported outcomes.

In previous studies with rasagiline, adverse events with MAOB-I monotherapy in early PD have generally been reported as mild and infrequent. In the TEMPO [(TVP-1012) in Early Monotherapy for Parkinson's Disease Outpatients] study involving patients with early PD, where rasagiline was compared to placebo in a multicenter, randomized, controlled trial over 26 weeks, the incidence of adverse events in the rasagiline group was not found to be any greater than in the placebo group[1,2,11].

Both investigator and patient-reported outcomes indicated that rasagiline had fewer associated gastrointestinal

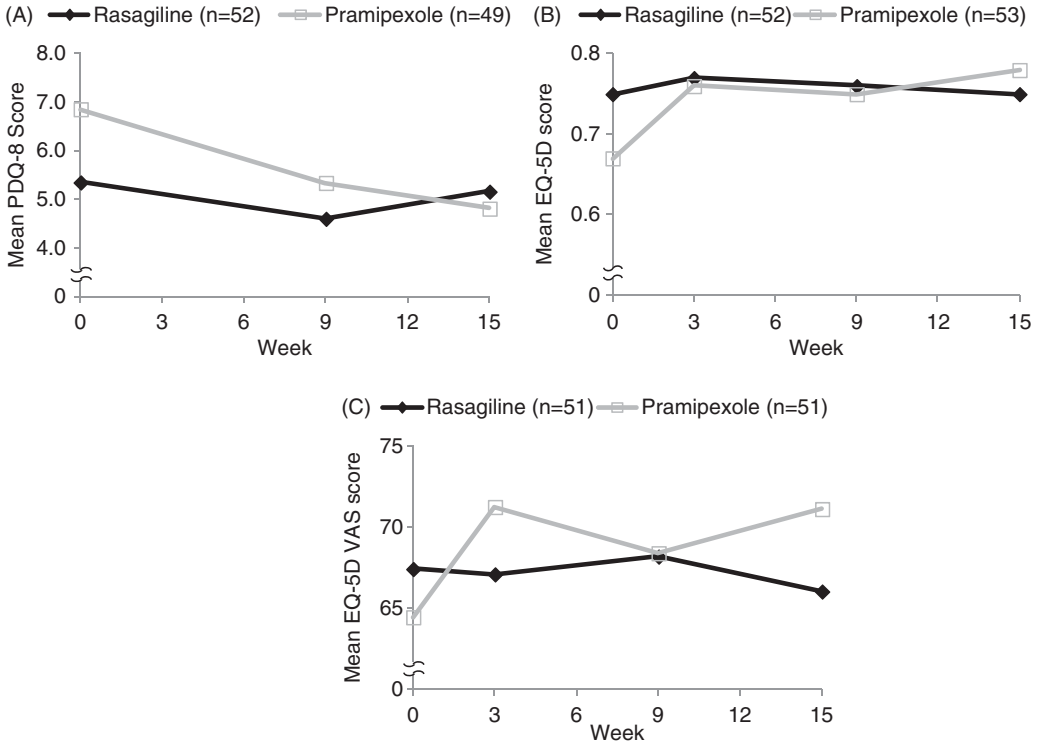

Figure 3. Mean quality of life score at each visit as measured by (A) PDQ-8 Score, (B) EQ-5D Score and (C) EQ-5D VAS Score (LOCF analysis).

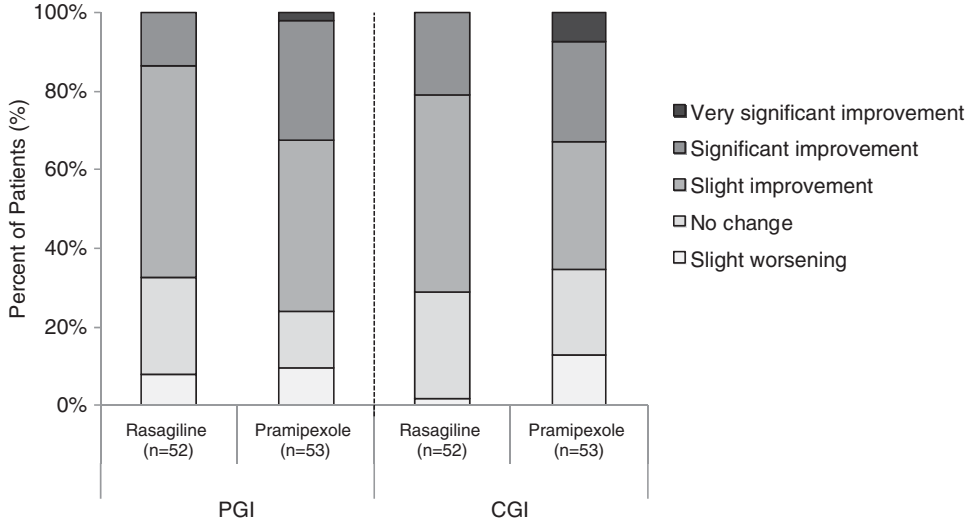

Figure 4. Symptom improvement measured by the PGI-I and CGI-I at week 15.

side-effects than pramipexole. Nausea and vomiting are common side-effects of PD treatment, but can often be mild and manageable. In this study over half of patients taking pramipexole reported nausea, with 23% of patients classifying the events as moderate to severe. Digestive difficulties were also reported with a significantly higher frequency in the pramipexole group, according to both physician and patient assessment.

Sleep disorders are also a very common adverse event associated with PD treatment, including excessive sleepiness, sleep fragmentation and sleep-onset insomnia, with the prevalence of somnolence estimated at approximately 30% of patients treated with dopamine agonists[12]. The MAO-B inhibitor selegiline has previously been associated with increased wakefulness and sleep-onset insomnia due to stimulation from an

amphetamine metabolite[13]. In this study rasagiline, which is not metabolized to amphetamines[14], was shown to significantly improve propensity to sleepiness during the monitoring period, and a decrease from baseline was observed in the number of patients reporting daytime sleepiness.

Compulsive behaviors have previously been reported in patients with PD, including pathologic gambling, hypersexuality, punding and compulsive shopping; the estimated lifetime prevalence of these behaviors is 13.7% in patients taking dopamine agonists such as pramipexole[12]. This was reflected in the results of this study, where more patients in the pramipexole group, compared to the rasagiline group, reported gambling and spending more than usual, and significantly more patients reported hypersexuality. These 'impulse control' disorders can frequently escape diagnosis, and can have a notable negative impact on quality of life and social functioning[15]. As dopamine is a key neurotransmitter in the reward pathways of the brain, the mechanism for the development of these behaviors is thought to be due to overstimulation of these pathways, particularly through the D_3 receptor, although the mechanisms are not well understood[12]. As pramipexole exhibits multiple receptor effects, including activity at the D_3 receptor, there is a high risk that it may induce compulsive behaviors in a dose-responsive manner[16].

The clinical effectiveness of the two treatments was assessed using both the clinician completed CGI- and patient completed PGI-I; a comparison of the scores in the two groups did not reveal any significant differences. Quality of life was assessed using the PDQ-8 and EQ-5D scales, although it was not possible to compare the treatment groups due to interaction between the covariate and the treatment. Intergroup analysis showed that quality of life improved with both treatments from baseline, stabilizing in the rasagiline group and continuing to improve in the pramipexole group.

The limitations of the ACTOR study include the limited sample size due to the lower than expected recruitment and the accidental inclusion of a patient who had taken contraindicated medication.

Conclusion

The results of this 15-week, non-inferiority analyzed, controlled study indicate that rasagiline is not inferior to pramipexole with regards to its safety and tolerability profile. However, the profile of rasagiline seems favorable, with fewer clinically important adverse events and with comparable effectiveness, as measured by both clinician and patient assessment.

Transparency

Declaration of funding

This study was funded in whole by Qualissima, who received a grant from Lundbeck.

Declaration of financial/other relationships

F.V. received honoraria from Qualissima for coordination of clinical centers. S.P., an employee of Qualissima received a grant from Lundbeck to carry out this study. S.L., an employee of Sylia Stat received payment from Qualissima for statistical analysis. O.B.'s official declaration of interest is available from the French Ministry of Health website www.sante.gouv.fr/declarations-publiques-d-interets.html. In addition, it should be noted that O.B. joined GSK after the study had been completed.

CMRO peer reviewers on this manuscript have no relevant financial relationships to disclose.

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Previous presentations

Outcomes of the ACTOR Study have previously been presented as posters at the following congresses:

(1) Viallet F, Pitel S, Lancrenon S, Blin O. A comparative study on safety and tolerability of rasagiline versus pramipexole in early Parkinson's disease (PD): The ACTOR study [abstract]: 15th EFNS Congress, Budapest, Hungary; September 10–13, 2011. *Eur J Neurol* 2011;18:344–620.

(2) Viallet F, Pitel S, Lancrenon S, Blin O. A comparative study on safety and tolerability of rasagiline versus pramipexole in early Parkinson's disease (PD): The ACTOR study [abstract]. 16th International Congress of Parkinson's Disease and Movement Disorders, Dublin, Ireland; June 17–21, 2012. *Mov Disord* 2012;27(Suppl 1):450.

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