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Efficacy and safety of adjunctive rasagiline in Japanese Parkinson's disease patients with wearing-off phenomena: A phase 2/3, randomized, double-blind, placebo-controlled, multicenter study

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ABSTRACT

Introduction: Rasagiline, a selective, irreversible monoamine oxidase-B inhibitor, is in development in Japan as adjunctive therapy to levodopa. This Phase 2/3 trial evaluated the efficacy and safety of adjunctive rasagiline in Japanese patients with Parkinson's disease (PD) and wearing-off phenomena.

Methods: Patients aged 30–79 years with diagnosed PD and stable levodopa use were randomized 1:1:1 to rasagiline (0.5/1 mg/day) or placebo for 26 weeks. The primary endpoint was change from baseline in mean daily OFF-time during the treatment period.

Results: In total, 141, 134, and 129 patients were randomized to placebo, rasagiline 0.5 mg, or rasagiline 1 mg, respectively. Baseline characteristics were well balanced. Least squares (LS) mean differences vs. placebo for change from baseline in mean daily OFF-time were −0.84 h (rasagiline 1 mg/day) and −0.60 h (rasagiline 0.5 mg/day); both differences were statistically significant. LS mean differences vs. placebo for change from baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II and Part III total scores (in ON-state) and Parkinson's Disease Questionnaire-39 Summary Index Score were: −1.27, −1.74, and −2.51 (0.5 mg/day) and −1.27, −2.14, and −3.84 (1 mg/day); all statistically significant. Treatment-emergent adverse events (TEAEs) occurred in 50.4/69.9/73.6% of the placebo, 0.5 mg/day, and 1 mg/day groups, respectively (most common TEAEs were nasopharyngitis [9.2/18.0/14.7%] and dyskinesia [7.1/8.3/16.3%]).

Conclusions: As an adjunct to levodopa, rasagiline reduced OFF-time and improved PD symptoms/signs (MDS-UPDRS scores) and quality of life in Japanese patients with PD and wearing-off phenomena. No important safety concerns were raised.

1. Introduction

Parkinson's disease (PD) is a degenerative disorder of the central nervous system [1] characterized by loss of dopaminergic neurons in the substantia nigra pars compacta [2], primarily affecting older individuals [3]. The prevalence of PD in Japan has been estimated at between 100 and 150 per 100,000 people [4–6], with peak age of onset over 50 years of age [3,4]. While incidence has not changed over time, prevalence has increased [5] due to the ageing of the population and, potentially, the longer lifespan of patients with PD.

Treatment for PD differs according to patient age, disease stage, most problematic symptoms, and the balance between efficacy and risk of adverse effects [1]. Guidelines of the Japanese Society of Neurology (2011) recommend that treatment of symptomatic PD begins with levodopa or a dopamine agonist [7]. While levodopa is effective in relieving PD symptoms [1], many patients receiving levodopa experience 'wearing-off' phenomena, due to reduced duration of therapeutic benefit of each levodopa dose [8]. Wearing-off and dyskinesia increase as duration of levodopa treatment increases [8].

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Wearing-off affects around 45% of Asian PD patients [8,9]. Factors associated with increased risk of wearing-off in Japanese patients include earlier onset, female gender, levodopa dosage, and duration of disease before commencing levodopa [9]. Wearing-off usually involves motor rather than non-motor symptoms, with slowness of movement and reduced dexterity being most common [8,10]; in one Chinese study, incidences were 83% and 67%, respectively [8,10]. Pain/aching was the most common non-motor symptom, affecting around a third of the patients [8]. As both wearing-off and dyskinesia impair daily living and reduce quality of life [8,10], effective management is extremely important.

European, Japanese and US guidelines recommend that wearing-off is managed by adjusting the dose/formulation of levodopa, or via adjunctive pharmacotherapy [1,7,11]. Commonly used adjunctive treatments include dopamine agonists, and drugs that potentiate effects of levodopa, such as catechol-O-methyltransferase (COMT) inhibitors (e.g. entacapone, tolcapone) and monoamine oxidase-B inhibitors (MAOB-I: e.g. selegiline, rasagiline) [1,8,12,13]. A large meta-analysis showed that such therapies reduce the duration of wearing-off phenomena (OFF-time), and alleviate symptoms [13]. Istradefylline and zonisamide are also used adjunctively in Japan, having been reported to reduce OFF-time and improve motor symptoms [7,14–16].

Rasagiline is a second-generation selective MAOB-I used both as monotherapy and combination therapy for PD [17]. Rasagiline is indicated outside Japan as adjunctive therapy for PD, based on findings from two Phase 3 studies in patients with wearing-off phenomena during treatment with levodopa [18,19]. To date, no controlled studies have evaluated rasagiline in Japanese PD patients with wearing-off phenomena. This study evaluated the efficacy and safety of adjunctive rasagiline in Japanese PD patients with wearing-off phenomena while receiving levodopa.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, Phase 2/3 trial of the efficacy and safety of adjunctive rasagiline in Japanese patients with PD and wearing-off phenomena while receiving levodopa. The study was conducted at 68 sites in Japan (January 2015 to September 2016). Following a 2-week run-in period, during which patients continued to receive levodopa (at least three times daily) at the dose they were receiving before trial entry, patients who met inclusion and exclusion criteria were randomized 1:1:1 to treatment with once-daily oral rasagiline (0.5 or 1 mg/day) or placebo for 26 weeks. During weeks 0–6, the levodopa dose could be reduced by the investigator, if needed due to adverse events (after week 6, the dose could not be changed). Patients could continue concomitant treatment with other PD agents, including dopamine agonists, anticholinergic drugs, amantadine, droxidopa, istradefylline, or zonisamide, provided the dose had not changed in the 14 days before the start of the run-in period. Entacapone was permitted, provided the dose was not altered after the start of the run-in period (dose modifications were allowed if dose of levodopa was changed between weeks 0 and 6). Treatments were administered before or after breakfast. Patients used a home diary to record ON-time with and without troublesome dyskinesia, OFF-time, and sleeping time, at 30-minute intervals for 24 h during the 7 days preceding the week 6, 14, and 26 visits. Patients were also required to complete the diary for at least 4 of the 7 days preceding the visit at the end of the run-in period. Patients received instructions from the investigators on how to complete the diary.

Full institutional review board approval was obtained at each study site, and all patients provided written, informed consent. This study was conducted with the highest respect for the study participants according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization unified guidelines and regulatory requirements of the region, and was registered with ClinicalTrials.gov (NCT02337738).

2.2. Patients

Adults aged 30–79 years with PD (UK Parkinson's Disease Society Brain Bank diagnostic criteria) were eligible for the study. All patients had been continuously receiving levodopa plus a dopa decarboxylase inhibitor for at least 6 months before the run-in period, and were experiencing wearing-off phenomena. At baseline, eligible patients had a modified Hoehn & Yahr stage score [20] of 2–4 in the OFF state, and mean OFF-time of $\geq$2.5 h per day. Among the exclusion criteria were: severe dyskinesia or unstable systemic disease; Mini-Mental State Examination score $\leq$24 at the start of the run-in period; and neurosurgery for PD.

2.3. Endpoints and assessments

The primary endpoint was the change from baseline in mean daily OFF-time during the treatment period, calculated as the difference between the baseline mean daily OFF-time and the mean OFF-time for a total of 21 days, consisting of three separate 7-day periods preceding the visits at week 6, 14, and 26 of the treatment period. Baseline mean daily OFF-time was calculated as the mean for the 7 days preceding the visit at the end of the run-in period.

Secondary endpoints included the mean daily OFF-time for each visit, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [21] Part II (motor aspects of activities of daily living) total score, the Part III (motor examination) total score (ON-state), and the Parkinson's Disease Questionnaire (PDQ-39) Summary Index score [22] and individual domain scores. Additional endpoints were daily ON-time without troublesome dyskinesia, and the MDS-UPDRS Part I and Part IV total scores.

Secondary and additional endpoints, except PDQ-39, were expressed as changes from baseline to weeks 6, 14, and 26. PDQ-39 was expressed as change from baseline to weeks 14 and 26. MDS-UPDRS was evaluated by accredited investigators or by patients [21]. Lower scores indicate milder PD symptoms/signs. PDQ-39 is a self-reported questionnaire that assesses quality of life; lower scores indicate better quality of life.

Safety was mainly assessed by evaluating the incidence of treatment-emergent adverse events (TEAEs), classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. TEAEs were defined as events occurring from the time of the first administration of study drug in the treatment period until week 26 (or at early termination). An additional safety endpoint was the change from baseline in mean daily ON-time with troublesome dyskinesia.

2.4. Statistical analysis

The primary efficacy endpoint of change from baseline in mean daily OFF-time during the treatment period was analyzed using an Analysis of Covariance (ANCOVA) model, with treatment group and baseline mean daily OFF-time as factors. Pairwise comparisons between rasagiline (1 and 0.5 mg/day) and placebo were conducted, based on the above model. Similar analyses were performed for all secondary and additional endpoints; the last-observation-carried-forward (LOCF) method was used for these endpoints, for the 26-week time point. For the primary endpoint, multiplicity was accounted for via a closed testing procedure for comparisons between treatment groups. Safety data were summarized using descriptive statistics. The change in mean daily ON-time with troublesome dyskinesia was analyzed using an ANCOVA model with treatment group and mean daily ON-time with troublesome dyskinesia at baseline as factors.

A two-sided test with 5% significance was applied. The intended sample size of 133 patients per group (total samples, 400) was chosen to provide at least 90% power to detect an improvement of 0.90 h or more in the mean total daily OFF-time in the 1 mg rasagiline group, compared with the placebo group (assuming a common standard