

RASAGILINE IN ADVANCED STAGE PARKINSON'S DISEASE

PLACEBO DATA ONLY IS AVAILABLE. SPECIFIC DATA RELATED TO STUDY TREATMENT IS NOT INCLUDED. (See PRESTO data dictionary)

Protocol number	TVP-1012/133 (PRESTO)
Protocol Title	A Multicenter, US and Canada, Double Blind, Randomized, Placebo-Controlled, Parallel Group Study, for the Efficacy, Tolerability and Safety of Rasagiline Mesylate in Levodopa Treated Parkinson's Disease Patients with Motor Fluctuations.
Clinical Phase	III
Study Centers	Approximately 45-50 PSG sites
Study Period	Planned duration of the study: 6 months (26 weeks) double blind. Planned enrollment duration: 12 months
Study Objective	To evaluate the efficacy, tolerability, and safety of 0.5 and 1 mg of rasagiline versus placebo in subjects with levodopa-treated Parkinson's disease (PD) and motor fluctuations.
Study Population	Outpatients with idiopathic PD who are experiencing motor fluctuations on levodopa therapy.
Study Design	Multicenter, double-blind, placebo-controlled study of parallel groups of PD subjects with motor fluctuations on levodopa therapy. Following a screening visit to ensure that subjects meet all enrollment criteria including accurate home diary completion, and home blood pressure monitoring, subjects will be randomized to one of 2 dosages of rasagiline or matching placebo. Levodopa dosage can be decreased during the first 6 weeks of the study period at the discretion of the investigator, and must remain constant for the last 20 weeks. Subjects will have visits 3, 6, 10, 14, 20, and 26 weeks after baseline for safety monitoring. A home diary in which subjects rate themselves as "ON without dyskinesias or ON without troublesome dyskinesias", "ON with troublesome dyskinesias", "OFF", or "asleep" every half hour will be completed for 3 days immediately prior to Baseline, Week 6, 14, and 26. Subjects will monitor blood pressures before and 45 minutes and 90 minutes after the main meal of the day for 7 days prior to Baseline, Weeks 3, and 26. When blood pressure monitoring and 24-hour diaries are both required before a visit, blood pressure monitoring should begin 10 days before the visit, so that diaries may be completed without distraction on the 3 days immediately prior to the visit.
Number of subjects	150 per group, 450 total.
Dose adjustment	Dosages of levodopa may be decreased at the discretion of the Investigator, in the event of intolerability, during the first 6 weeks of the study only. This may be accomplished by decreasing the amount of levodopa given per dose, by omitting a dose, or by increasing the interval between doses. If decreasing the dosage of levodopa leads

	<p>to a suboptimal response, the dosage may be increased back to the baseline dosage (during the first 6 weeks of the study only), but should <u>not</u> be increased above the baseline dosage. Dosages of other anti-Parkinson medications should not be changed during the study period. The dosage of entacapone should be changed only if the number of levodopa doses changes and only during the first 6 weeks of the study.</p>
<p>Inclusion Criteria</p>	<ol style="list-style-type: none"> 1. Men and women with idiopathic Parkinson's disease whose diagnosis is confirmed by at least two of the cardinal signs (resting tremor, bradykinesia, rigidity) being present, without any other known or suspected cause of parkinsonism. 2. Subjects must experience levodopa related motor fluctuations averaging at least 2.5 hours daily in the "OFF" state, confirmed by the baseline home diaries. 3. Modified Hoehn and Yahr stage < 5 in the "OFF" state. 4. Subjects must be taking optimized levodopa/carbidopa or levodopa /benserazide therapy (based on investigator's judgment), stable for at least 14 days prior to baseline. Subjects must be receiving at least 3 daily doses of levodopa, not including a bedtime dose. 5. Subjects who are treated with entacapone should be on stable doses for at least 14 days prior to baseline. The dosage of entacapone should only be changed during the study period if the number of levodopa doses changes. 6. Subjects who are treated with dopamine agonists and other anti-PD drugs should be on stable doses for at least 30 days prior to baseline. The dosage of dopamine agonists and other anti-PD drugs should remain constant throughout the study period. 7. Selegiline must be discontinued for at least 90 days prior to baseline. 8. Women must be postmenopausal, surgically sterilized, or using adequate birth control. Woman of childbearing potential must have a negative pregnancy test (serum beta-HCG) at screening. 9. Subjects must be age 30 or older. 10. Subjects must be withdrawn from tolcapone and antidepressants, including selective serotonin reuptake inhibitors, tricyclic, and tetracyclic antidepressants (except amitriptyline, trazodone, citalopram, paroxetine and sertraline at stable low dosages as outlined in Section 6.1 of the protocol) at least 42 days prior to baseline. 11. Subjects must be withdrawn from sympathomimetics (including over the counter (OTC) cold remedies - nasal or oral), dextromethorphan, pethidine, St. John's Wort and gentamicin at least 7 days prior to baseline. 12. Subjects must demonstrate the ability to keep accurate diaries of drug intake and Parkinson's disease symptoms prior to randomization; i.e. at least 75% concordance between subject and investigator/coordinator diary ratings must be achieved during the diary training session. Subjects must have at least one transition from "OFF" to "ON" or from "ON" to "OFF" during the training session. Subjects must be willing and able to complete adequate

	<p>diaries throughout the study period.</p> <p>13. Subjects must be willing and able to give informed consent.</p>
Exclusion Criteria	<p>Subjects with a clinically significant or unstable medical or surgical condition which would preclude safe and complete study participation. Such conditions may include cardiovascular, pulmonary, hepatic, renal, or metabolic diseases or malignancies as determined by medical history, physical exam, laboratory tests, chest x-ray, or ECG.</p> <p>Subjects with clinically significant or unstable vascular disease e.g.:</p> <ul style="list-style-type: none"> • clinically significant arrhythmia or valvular heart disease as judged by investigator. • congestive heart failure (New York Heart Association class 2 or greater) • significant ischemic heart or cerebrovascular disease (such as unstable angina pectoris, stroke or myocardial infarction within the last 6 months) • severe hypertension as defined in Appendix VIII (including after meals as noted on home blood pressure monitoring) • clinically significant orthostatic hypotension (and/or SBP change > 30 mmHg) • clinically significant syncope associated with hypotension within the past 2 years. <p>Subjects with significant cognitive impairment as defined by MMSE score ≤ 24.</p> <p>Subjects with clinically significant psychiatric illness, including depression (Beck [short form] depression scale ≥ 15), which compromises their ability to provide consent or participate fully in the study.</p> <p>Concomitant therapy with MAO inhibitors, reserpine, methyldopa within the past three months, or treatment with an anti-emetic or neuroleptic medication with central dopamine antagonist activity with the past six months.</p> <p>Subjects with a history of alcohol or substance abuse within the past 2 years.</p> <p>Subjects who have taken experimental medications within 60 days prior to baseline.</p> <p>Subjects who have undergone a neurosurgical intervention for Parkinson's disease [e.g., pallidotomy, thalamotomy, and deep brain stimulation (DBS)] within the 12 months preceding the Baseline visit. Subjects who have undergone neurosurgical transplantation are excluded regardless of when the procedure(s) was performed. No programming changes are permitted in subjects who have undergone DBS.</p> <p>Subjects with severe disabling dyskinesias.</p> <p>Subjects with known serious adverse reaction to selegiline.</p> <p>Subjects with known adverse reactions associated with ingestion of tyramine-containing food.</p> <p>Participation in a previous clinical trial of rasagiline.</p>
Route and Dosage Form	<p>Oral; rasagiline tablets or matching placebo in bottles, administered once a day in the morning 30 minutes before breakfast.</p>

Dosage	Rasagiline 0.5 mg, 1 mg, or placebo.
Primary efficacy endpoint	Change from baseline in the mean total daily “OFF” time, as measured by home diaries.
Secondary efficacy endpoints	<ul style="list-style-type: none"> a. Change in UPDRS, Part III (Motor) during “ON” state. b. Change in UPDRS, Part II (Activities of Daily Living, ADL) during “ON” state c. Change in UPDRS, Part II (ADL) during “OFF” state
Safety and tolerability endpoints	<p>1. Safety</p> <ul style="list-style-type: none"> a. Adverse event frequency and severity, changes in vital signs, clinical laboratory values. b. Change in duration of “ON with troublesome dyskinesia” time as measured with home diaries c. Change in UPDRS, Part I (Mental) d. Number of subjects with post prandial increases in systolic blood pressure of more than 30 mmHg, on one or more occasions, as recorded during home blood pressure monitoring. <p>2. Tolerability</p> <ul style="list-style-type: none"> a. Number of subjects who discontinue the study b. Number of subjects who discontinue the study due to AEs
Pharmacokinetics/ Pharmacodynamics	<ul style="list-style-type: none"> a. Population pharmacokinetics b. Platelet MAO-B activity (approximately 60 subjects at selected sites)
Exploratory Endpoints	<ul style="list-style-type: none"> a. Change in Clinical Global Evaluation Scale b. Change in Schwab and England ADL scale c. Change in levodopa dosage. d. Change in PD QUALIF
Sample Size Considerations	A total of 450 patients, equally randomized to the three treatment groups, will provide a power of between 84% and 94% (at 5% significance level), to detect a statistically significant difference, when the true effect of the 1 mg dose compared to placebo is 45 minutes, and the true effect of the 0.5 mg dose compared to placebo is between 0 minutes and 45 minutes.
Statistical Analysis	A total of approximately 450 patients will be equally randomized into the 3 treatment arms. Randomization will stratify patients by centers. The principal statistical analysis of the primary endpoint will be an Analysis of Covariance (ANCOVA) accounting for baseline mean total daily “OFF” time.