

TEMPO

PROTOCOL SYNOPSIS

Rasagiline Mesylate (TVP-1012) in Early Monotherapy for PD Outpatients

(Prepared by the Parkinson Study Group (PSG) with the Support of
Teva Pharmaceutical Industries, Ltd.)

PLEASE NOTE: Teva has agreed to share the placebo data only.
Therefore the Active Treatment Phase data is not included since all subjects
were on rasagiline during this phase.

Protocol number	TVP/1012/232
Protocol Title	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Phase III Clinical Trial for The Efficacy, Tolerability and Safety of Two Doses of Rasagiline Mesylate in Early Parkinson's Disease (PD) Patients Not Treated with Levodopa.
Clinical Phase	III
Investigators	Parkinson Study Group (PSG)
Study Centers	32 PSG study centers in the U. S. and Canada (Coordinating and Biostatistics Centers at University of Rochester)
Study Period	Planned duration of the study: 6 months double-blind 6 months active treatment Planned enrollment duration: 12 months
Study Objective	To compare with placebo the efficacy, tolerability and safety of low and high dosages of Rasagiline in early PD patients not treated with levodopa.
Study Population	Early PD patients in H/Y Stage ≤ 3.0 in the U. S. Early PD patients in H/Y Stage < 3.0 in Canada.

<p>Study Design</p>	<p>Multicenter, double-blind, placebo-controlled study with parallel groups of outpatients with early PD. Patients will be randomized to one of two (low or high) dosages of Rasagiline or placebo. There will be a 1-week titration phase, followed by a 25-week maintenance phase and a 6-month active treatment extension which includes a blinded 1 week titration period. Subjects will not know whether they are on 1mg/day or 2mg/day during the extension. Subjects previously receiving rasagiline in the double-blind will maintain the same dose during the extension. Subjects previously receiving placebo during the double-blind will begin a dose of 1 mg/day and titrate up to 2mg/day after 1 week.</p> <p>Subjects receiving rasagiline during the double-blind period, who require additional therapy, will maintain the same dose of rasagiline during a 1 week sham titration upon entering the extension. If requiring additional therapy after a total exposure to rasagiline of 2 weeks, these subjects will be seen at an unscheduled visit to begin therapy with either levodopa or a marketed dopamine agonist.</p> <p>Subjects entering the extension who were previously on placebo, who require additional therapy, will begin a dose of 1 mg/day and titrate up to 2 mg/day after 1 week. If requiring additional therapy after a total exposure to rasagiline of 2 weeks, these subjects will be seen at an unscheduled visit to begin therapy with either levodopa or a marketed dopamine agonist.</p>
<p>Number of Patients</p>	<p>Total number of patients estimated is: ~120/group or total N = 360</p>

**Diagnosis and Main
Inclusion Criteria**

- 1) Men and women with idiopathic Parkinson's disease (PD) whose diagnosis is confirmed by at least two of the cardinal signs (resting tremor, bradykinesia, rigidity) being present, without other known or suspected cause of parkinsonism. Subjects with predominant tremor may be included.
- 2) Women must be postmenopausal, surgically-sterilized, or using adequate birth control (barrier methods alone are not adequate). Women of childbearing potential must have a negative pregnancy test (serum beta-HCG test) upon entry into the study.
- 3) Patients must be age 35 years or older.
- 4) Modified Hoehn and Yahr stage \leq 3.0.
- 5) Patients not taking or requiring anti-parkinsonian medications, except for anticholinergics.
 - a. stable for at least 42 days off of levodopa, dopamine agonists and amantadine prior to baseline.
 - b. stable dose of anti-cholinergics or specified antidepressants for at least 60 days prior to baseline, and such dosages must remain stable throughout the study.
 - c. APPLIES TO CANADIAN SITES ONLY: Subjects previously treated with levodopa or dopamine agonists must have discontinued them for at least 42 days prior to being considered for the study. Subjects must not be withdrawn from levodopa or dopamine agonists expressly for inclusion in the study.
- 6) Selegiline must be discontinued for at least 90 days prior to baseline.
- 7) Subjects must be withdrawn from fluoxetine hydrochloride (Prozac®), other antidepressants [with the exception of amitriptyline, trazadone, sertraline (Zoloft®), paroxetine (Paxil®) and fluoxamine maleate (Luvox®)] for at least 42 days prior to baseline.
 - ❑ Subjects must be withdrawn from meperidine (pethidine) for at least 42 days prior to baseline.
 - ❑ Subjects must be withdrawn from dextromethorphan (DM) for at least 7 days prior to baseline.
- 8) Patients must be withdrawn from sympathomimetics (including over the counter (OTC) cold remedies – oral or nasal) for at least 7 days prior to baseline.
- 9) Subjects must be withdrawn from gentamicin for at least 14 days prior to baseline.
- 10) Subjects must be withdrawn from St. John's Wort for at least 14 days prior to baseline.

<p>Exclusion Criteria</p>	<ol style="list-style-type: none"> 1) Patients with unstable systematic medical problems or clinically significant malignancy, with particular attention to clinically significant or unstable vascular disease (e.g.): <ul style="list-style-type: none"> - clinically significant arrhythmia or valvular heart disease as judged by investigator - congestive heart failure (NYHA 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 - clinically significant orthostatic hypotension (and/or SBP change > 30 mmHg) - clinically significant syncope associated with hypotension within the past 2 years 2) Patients with dementia as defined by MMSE score \leq 23 3) Patients with clinically significant psychiatric illness which compromises their ability to provide consent or participate fully in the study 4) Patients with major/severe depression 5) Patients who have abnormal clinically significant laboratory test results 6) Patients who abuse substances or drugs 7) Patients with known serious adverse reaction to selegiline (deprenyl) 8) Patients with known adverse reaction associated with ingestion of tyramine-containing food 9) <u>Participation in another clinical trial during the previous 60 days or taking any experimental drug within the past 90 days.</u> <u>Participation at any time in an earlier trial of rasagiline.</u>
<p>Route and Dosage Form</p>	<p>Oral; Rasagiline (tablets) and matching placebo supplied in bottles. Administered once a day in the morning (at least 30 minutes prior to a meal).</p>

Dosages Treatment Arms	1 mg/d, 2 mg/d placebo, 1 mg/d, 2 mg/d
Dosage Reductions	In the event of intolerability during the double-blind phase, there will be no dosage reductions. Patients requiring dosage reduction will be terminated from the study. During the extension phase one dose reduction to a half tablet will be allowed. There will be no dose increases.
Duration of Treatment	The duration of treatment of Rasagiline or placebo is a 1-week titration period, 25 weeks of maintenance therapy, followed by a 6-month active treatment extension.
Primary Outcome Measures	<p>A. Efficacy</p> <p>a) Change in mean total UPDRS score between treatment and placebo (calculated from baseline to 26 weeks)</p> <p>B. Tolerability</p> <p>a) Number of patients completing study on their original treatment assignment</p> <p>C. Safety</p> <p>a) Change in adverse event frequency, vital signs (increase in blood pressure), clinical laboratory values</p>
Secondary Outcome Measures	<p>A. Efficacy</p> <p>a) Repeated measures analysis of covariance of the total UPDRS</p> <p>b) Change in individual components of the UPDRS (i.e., mental, motor, and ADL) from baseline to 26 weeks</p> <p>c) Need for levodopa therapy</p> <p>d) Proportion of levodopa-free patients at 26 weeks</p> <p>e) Change in Hoehn & Yahr and Schwab and England ADL from baseline to 26 weeks</p> <p>f) Change in timed motor tests from baseline to 26 weeks</p> <p>g) Clinical Global Impression (CGI) stratified by center</p> <p>h) Change in Quality of Life (QOL) measurement from baseline to 26 weeks</p>
Sample Size Considerations	A sample size of 120 per group gives 75%-88% power to detect (at 0.05 significant level) a relative improvement of 3 UPDRS points or greater between rasagiline and placebo from baseline to week 26.