

RAPID PROTOCOL SYNOPSIS

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

Protocol Number	TV-1203/111
Protocol Title	A Multicenter, Randomized, Double-Blind, Double Dummy, Parallel Group Study Comparing TV-1203/Carbidopa (TV-1203/CD) Dispersible Tablets with Levodopa/Carbidopa (LD/CD) Tablets in Advanced Parkinson's Disease (PD) Patients with Motor Fluctuations
Clinical Phase	Phase III
Study Centers	About 42 study centers – USA/Canada (Parkinson's Study Group – CTCC – Clinical Trials Coordination Center)
Study Period	Planned duration of study: 20-24 weeks <ul style="list-style-type: none"> • 2-6 week LD/CD open-label run-in period • 18-week double blind treatment phase (dose adjustments are allowed the first 8 weeks)
Study Objectives	To evaluate the efficacy, safety and tolerability of TV-1203/CD dispersible tablets in PD patients with motor fluctuations treated with chronic LD/CD therapy.
Study Population	PD patients with motor fluctuations on chronic LD/CD therapy
Study Design	<p>Multicenter, randomized, double-blind, double dummy, comparative study with parallel groups of PD patients experiencing motor fluctuations on chronic LD/CD or levodopa/benserazide (LD/BZD) therapy.</p> <p>There will be a period of 2-6 weeks following the screening visit where potential subjects will start an open-label run-in period by replacing their daily immediate release LD/CD or LD/BZD doses with the formulation of LD/CD (4:1) tablets that will be used in the following double-blind treatment phase. Eligible subjects who have maintained an optimal and stable dose of the LD/CD in the run-in period for at least 2 weeks and adequately completed a total of 6 days of diaries, i.e., 3 days each of the "24 Hour" and "Time to ON" diaries (at the end of the run-in period), will be randomized in a 1:1 ratio to one of the following groups:</p> <ol style="list-style-type: none"> 1) TV-1203/CD dispersible tablets + placebo for LD/CD tablets 2) LD/CD tablets + placebo for TV-1203/CD dispersible tablets <p>The duration of the treatment (double-blind) phase will be 18 weeks, when dose adjustment is allowed during the first 8 weeks. All daily immediate release LD/CD doses (4:1 ratio) will be replaced by the equivalent doses of study drugs.</p> <p>Subjects will be evaluated at the study centers at screening (Sc), baseline (week 0) and at weeks 4, 8, 13 and 18 (total of 6 visits). Two mandatory telephone follow-ups will occur as follows:</p> <ol style="list-style-type: none"> 1. During the first 2 weeks after screening visit (run-in period) for assessment of the need for LD/CD (4:1) dose adjustment.

	<p>2. One to two weeks after randomization for assessment of the need for study drug dose adjustment.</p> <p>Diaries will be completed sequentially by subjects as follows: Three days of “24-Hour” diaries followed by three days of “Time to ON” diaries for a total of 6 days of diary recording prior to the baseline visit and prior to the week 18 visit.</p> <p>Additionally, two days of “24-Hour” diaries followed by two days of “Time to ON” diaries for a total of 4 days of diary recording will be completed prior to the week 8 and week 13 visits.</p> <p>No changes in study drug dosing regimen are allowed during the 6 or 4 days of diary recording throughout the study or during the last 10 weeks of the study.</p> <p>The diaries will be completed in order to measure:</p> <ol style="list-style-type: none"> 1. “Time to ON” of daily doses 2. Total daily “OFF Time” 3. Dyskinesias (troublesomeness and duration) <p>At week 18 (termination visit) pharmacokinetic (PK) measurements will be conducted for population PK.</p>
Dose Adjustments	<p>During the first 8 weeks of study drug treatment (excluding the 4 days of diary recording), in the event of intolerability or suboptimal therapeutic response, individual dosages may be decreased or increased (by as little as ¼ tablet), the time interval between doses may be lengthened or shortened (to a minimum of 90 minutes) or the number of daily doses may be increased or decreased by one dose.</p>
Number of Patients	<p>About 300, without replacements for early terminations/withdrawals (approximately 8 per site)</p>
Diagnosis and Main Inclusion Criteria	<ol style="list-style-type: none"> 1. Men and women with idiopathic Parkinson’s disease whose diagnosis is defined by the presence of at least two of the cardinal PD signs (resting tremor, bradykinesia, rigidity). 2. Hoehn and Yahr stage less than 5 in the “OFF” state. 3. Chronic therapy with immediate release LD/CD or levodopa/benserazide (LD/BZD) which is complicated by motor fluctuations (e.g. delayed ON, dose failures, wearing OFF). 4. Patients must be on a minimum daily dosage of levodopa of 300mg and must be receiving at least 4 daily doses of immediate release 4:1 LD/CD or LD/BZD. Prior to baseline, the interval between LD/CD doses must be ≥ 2 hours. Where available, LD/BZD is allowed <i>only</i> prior to the Screening visit. Either combination product, LD/CD or LD/BZD, may be in ratios of 4:1 or 10:1, but only
	<p>prior to the Screening visit. Once the patient has begun Run-in, only 4:1 LD/CD is allowed. LD/CD must be maintained at an optimal and stable dosage (based on investigator judgment) for a minimum of 2 weeks prior to the baseline visit (run-in period). Use of sustained release LD/CD (e.g. Sinemet[®] CR) is allowed during the day only in combination with immediate release LD/CD formulation; a doses of Sinemet[®] CR taken alone at bedtime or later during the night are is</p>

	<p>allowed, but must remain unchanged throughout the study with regard to timing and dosage. The minimum daily dosage of levodopa, 300 mg must come from an immediate release formulation. For those subjects who switch from Sinemet® CR to immediate release LD/CD prior to screening, it is recommended that they be maintained on the new immediate release LD/CD regimen for a minimum of two weeks prior to the screening visit.</p> <ol style="list-style-type: none"> 5. Patients must have ≥ 30 minutes “delayed ON” time for at least 1 dose per day and an average total “delayed ON” time (including dose failures) following all daily LD/CD doses of at least 90 minutes per day, based on the 3 days of diaries completed prior to the baseline visit. 6. Patients must have an average of at least 2.5 hours of total “OFF” time per day during the waking hours, based on the 3 days of diaries completed prior to the baseline visit. 7. Age ≥ 30. 8. Women must be postmenopausal or using adequate birth control methods. Women of childbearing potential must have a negative pregnancy test at screening. 9. Concomitant therapy is permitted with marketed dopamine agonists, entacapone, amantadine, selegiline, and anticholinergic agents. All concomitant PD medications must be maintained at stable dosages for at least 4 weeks prior to the baseline visit and throughout the duration of the study, except for entacapone for which the number of doses may increase or decrease to correspond with LD/CD or TV-1203/CD dosing. 10. Patients must demonstrate the ability to keep accurate diaries of drug intake, dose responses, and activity prior to randomization; i.e. a 75% concordance rate between patient and investigator/coordinator “24-hour” diary ratings must be achieved during the diary training sessions. Patients must have at least one transition from “OFF” to “ON” during the training session. Patients must correctly complete the “Time to ON” diary entries for one dosing cycle. Patients must be able and willing to continue to keep adequate diaries throughout the treatment period. 11. Patients must be willing and able to give informed consent.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Patients 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, metabolic diseases or malignancies as determined by medical history, physical exam, laboratory tests, chest x-ray, or ECG. For clinically significant abnormal values of hepatic and renal function tests see Appendix III. 2. Patients with a history of malignant melanoma. 3. Patients with narrow angle glaucoma. 4. Known hypersensitivity, allergy, or contraindication to levodopa or carbidopa. 5. Patients treated with doses of Sinemet CR® alone (i.e., without immediate release Sinemet) during the day (excluding doses taken at bedtime or later during the night which must remain unchanged throughout the study with regard to timing and dosage). 6. Patients treated with tolcapone within 4 weeks prior to starting the baseline diaries. 7. Concomitant therapy with MAO inhibitors (except selegiline),

	<p>reserpine, methyldopa within the past three months, or treatment with an anti-emetic or neuroleptic medication with central dopamine antagonist activity within the past six months.</p> <ol style="list-style-type: none"> 8. Patients with a recent history (≤ 2 years) of substance abuse. 9. Patients with a MMSE score ≤ 24. 10. Patients with a clinically significant psychiatric illness, including depression, which compromises their ability to provide consent or participate fully in the study. 11. Participation in another investigational drug trial during the previous 60 days prior to baseline. 12. Patients who have participated in a previous clinical trial of TV-1203. 13. Patients who have undergone fetal cell transplantation. 14. Patients who have undergone unilateral or bilateral neurosurgery for PD [pallidotomy, thalamotomy or implantation of electrodes for deep brain stimulation (DBS)] within the 12 months preceding the Baseline visit. 15. Patients who have had DBS programming changes within 1 month prior to the Screening visit or who can expect to have changes in the DBS programming during the course of the study.
Route and Dosage Form	Oral tablets, swallowed whole; TV-1203/CD (114mg/25mg) dispersible tablets with matching placebo tablets; LD/CD (100mg/25mg) tablets with matching placebo tablets
Treatment Arms	<ol style="list-style-type: none"> 1. TV-1203/CD dispersible tablet + placebo for LD/CD tablet 2. LD/CD tablet + placebo for dispersible TV-1203/CD tablet
Duration of Treatment	The total duration of double blind study drug treatment is 18 weeks. (dose adjustment is allowed during the first 8 weeks)
Run-in treatment	LD/CD (4:1) tablets (open-label)
Duration of run-in treatment	LD/CD run-in duration is between 2 to 6 weeks, i.e. LD/CD must be at an optimal and stable dose for a minimum of 2 weeks prior randomization
Primary Outcome Measure	The mean time to reach "ON" state of doses taken at "OFF" state will be calculated separately for diaries recorded prior to randomization and for those measurements during the 18 weeks of double blind treatment. The difference between these two measures is identified as the change from baseline in mean "Time to ON" of doses taken at "OFF" state.
Complementary Analyses to the Primary Outcome Measure	<p><u>Efficacy:</u></p> <ol style="list-style-type: none"> 1. Change from baseline in mean "Time to ON" of doses taken at OFF state, at termination visit. 2. Percent of "Time to ON" responders; i.e. patients with a decrease in mean "Time to ON" of doses taken at OFF state of at least 10 minutes.
Secondary Outcome Measures	<p><u>Efficacy:</u></p> <ol style="list-style-type: none"> 1. Change from baseline in mean total daily "OFF" time during the waking hours (non-inferiority). 2. Change from baseline in the mean total daily "ON" time with no dyskinesia or without troublesome dyskinesia. <p>Percent of "dose failure" episodes as defined by failure to "turn on" within 90 minutes following dosing.</p>
Tolerability	<ol style="list-style-type: none"> 1. Number of patients completing the 18 weeks of double blind treatment. 2. Number of patients discontinued the study due to adverse experiences.
Safety	<ol style="list-style-type: none"> 1. Dyskinesia: Change from baseline in Lang/Fahn Dyskinesia Scale Change from baseline in daily duration of ON with troublesome dyskinesias from diaries

	<p style="text-align: center;">Change from baseline in UPDRS Part IV, Dyskinesias</p> <ol style="list-style-type: none"> 2. Assessment of adverse events, vital signs and clinical laboratory measurements. 3. Assessment of ECG and vital signs relative to study drug dosing.
Population Pharmacokinetics	<ol style="list-style-type: none"> 1. Assessment of levodopa and carbidopa profiles in treatment group. 2. Determination of the presence of TV-1203 levels.
Exploratory Outcome Measures	<ol style="list-style-type: none"> 1. Change in UPDRS (total, motor and ADL subscales) and Schwab and England Scale (patient and investigator) 2. Categorical change from baseline of percent of dose failure episodes (out of total number of doses taken at "OFF" state). Dichotomization according to a cut-off point of an absolute reduction of 10% or more. 3. Change in Global Evaluation (patient and investigator.) 4. Dose regimen change in total daily study drug doses: <ol style="list-style-type: none"> a. Change from baseline in number of daily study drug doses at the end of week 8 of double blind treatment. b. Change from baseline in the total daily study drug dose at the end of week 8 of double blind treatment..
Statistical Methods and Sample Size Considerations	<p>A total of approximately 300 patients will be equally randomized into the 2 treatment arms. Randomization will stratify patients by centers.</p> <p>The principal statistical analysis of the primary outcome measure will employ the Analysis of Covariance accounting for baseline "Time to ON" (for doses taken while OFF) measurements and for the number of daily LD doses consumed prior to randomization as covariates.</p> <p>To fully establish the beneficial effect of TV-1203 an analysis with the aim of demonstrating non-inferiority with regard to total daily OFF time will also be performed.</p> <p>A total of 300 patients equally randomized to the two treatment groups will provide:</p> <ul style="list-style-type: none"> • 90% power for detecting a statistically significant difference of 4 minutes or more in the primary outcome measure. • 90% power to detect non-inferiority (at non-inferiority threshold of 45 minutes) of TV-1203/CD treatment as compared to a standard LD/CD treatment in the change from baseline of total daily OFF time.
Exclusion Criteria	<ol style="list-style-type: none"> 12. Patients 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, metabolic diseases or malignancies as determined by medical history, physical exam, laboratory tests, chest x-ray, or ECG. For clinically significant abnormal values of hepatic and renal function tests see Appendix III. 13. Patients with a history of malignant melanoma. 14. Patients with narrow angle glaucoma. 15. Known hypersensitivity, allergy, or contraindication to levodopa or carbidopa. 16. Patients treated with doses of Sinemet CR[®] alone (i.e., without immediate release Sinemet) during the day (excluding doses taken at bedtime or later during the night which must remain unchanged throughout the study with regard to timing and dosage). 17. Patients treated with tolcapone within 4 weeks prior to starting the baseline diaries.

	<p>18. Concomitant therapy with MAO inhibitors (except selegiline), reserpine, methyldopa within the past three months, or treatment with an anti-emetic or neuroleptic medication with central dopamine antagonist activity within the past six months.</p> <p>19. Patients with a recent history (≤ 2 years) of substance abuse.</p> <p>20. Patients with a MMSE score ≤ 24.</p> <p>21. Patients with a clinically significant psychiatric illness, including depression, which compromises their ability to provide consent or participate fully in the study.</p> <p>22. Participation in another investigational drug trial during the previous 60 days prior to baseline.</p> <p>16. Patients who have participated in a previous clinical trial of TV-1203.</p> <p>17. Patients who have undergone fetal cell transplantation.</p> <p>18. Patients who have undergone unilateral or bilateral neurosurgery for PD [pallidotomy, thalamotomy or implantation of electrodes for deep brain stimulation (DBS)] within the 12 months preceding the Baseline visit.</p> <p>19. Patients who have had DBS programming changes within 1 month prior to the Screening visit or who can expect to have changes in the DBS programming during the course of the study.</p>
Route and Dosage Form	Oral tablets, swallowed whole; TV-1203/CD (114mg/25mg) dispersible tablets with matching placebo tablets; LD/CD (100mg/25mg) tablets with matching placebo tablets
Treatment Arms	<p>3. TV-1203/CD dispersible tablet + placebo for LD/CD tablet</p> <p>4. LD/CD tablet + placebo for dispersible TV-1203/CD tablet</p>
Duration of Treatment	The total duration of double blind study drug treatment is 18 weeks. (dose adjustment is allowed during the first 8 weeks)
Run-in treatment	LD/CD (4:1) tablets (open-label)
Duration of run-in treatment	LD/CD run-in duration is between 2 to 6 weeks, i.e. LD/CD must be at an optimal and stable dose for a minimum of 2 weeks prior randomization
Primary Outcome Measure	The mean time to reach "ON" state of doses taken at "OFF" state will be calculated separately for diaries recorded prior to randomization and for those measurements during the 18 weeks of double blind treatment. The difference between these two measures is identified as the change from baseline in mean "Time to ON" of doses taken at "OFF" state.
Complementary Analyses to the Primary Outcome Measure	<p><u>Efficacy:</u></p> <p>2. Change from baseline in mean "Time to ON" of doses taken at OFF state, at termination visit.</p> <p>2. Percent of "Time to ON" responders; i.e. patients with a decrease in mean "Time to ON" of doses taken at OFF state of at least 10 minutes.</p>
Secondary Outcome Measures	<p><u>Efficacy:</u></p> <p>3. Change from baseline in mean total daily "OFF" time during the waking hours (non-inferiority).</p> <p>4. Change from baseline in the mean total daily "ON" time with no dyskinesia or without troublesome dyskinesia.</p> <p>Percent of "dose failure" episodes as defined by failure to "turn on" within 90 minutes following dosing.</p>
Tolerability	<p>3. Number of patients completing the 18 weeks of double blind treatment.</p> <p>4. Number of patients discontinued the study due to adverse experiences.</p>
Safety	<p>4. Dyskinesia: Change from baseline in Lang/Fahn Dyskinesia Scale Change from baseline in daily duration of ON with troublesome dyskinesias from diaries</p>

	<p style="text-align: center;">Change from baseline in UPDRS Part IV, Dyskinesias</p> <p>5. Assessment of adverse events, vital signs and clinical laboratory measurements.</p> <p>6. Assessment of ECG and vital signs relative to study drug dosing.</p>
Population Pharmacokinetics	<p>3. Assessment of levodopa and carbidopa profiles in treatment group.</p> <p>4. Determination of the presence of TV-1203 levels.</p>
Exploratory Outcome Measures	<p>5. Change in UPDRS (total, motor and ADL subscales) and Schwab and England Scale (patient and investigator)</p> <p>6. Categorical change from baseline of percent of dose failure episodes (out of total number of doses taken at "OFF" state). Dichotomization according to a cut-off point of an absolute reduction of 10% or more.</p> <p>7. Change in Global Evaluation (patient and investigator.)</p> <p>8. Dose regimen change in total daily study drug doses:</p> <ul style="list-style-type: none"> c. Change from baseline in number of daily study drug doses at the end of week 8 of double blind treatment. d. Change from baseline in the total daily study drug dose at the end of week 8 of double blind treatment..
Statistical Methods and Sample Size Considerations	<p>A total of approximately 300 patients will be equally randomized into the 2 treatment arms. Randomization will stratify patients by centers.</p> <p>The principal statistical analysis of the primary outcome measure will employ the Analysis of Covariance accounting for baseline "Time to ON" (for doses taken while OFF) measurements and for the number of daily LD doses consumed prior to randomization as covariates.</p> <p>To fully establish the beneficial effect of TV-1203 an analysis with the aim of demonstrating non-inferiority with regard to total daily OFF time will also be performed.</p> <p>A total of 300 patients equally randomized to the two treatment groups will provide:</p> <ul style="list-style-type: none"> • 90% power for detecting a statistically significant difference of 4 minutes or more in the primary outcome measure. • 90% power to detect non-inferiority (at non-inferiority threshold of 45 minutes) of TV-1203/CD treatment as compared to a standard LD/CD treatment in the change from baseline of total daily OFF time.