CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized Study Investigating the Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control (SUPPORT-PD™)
Protocol Number:	CVT-301-005
EudraCT Number:	2014-003799-22
US IND Number:	115750
Development Phase:	Phase 3
Study Sponsor:	Civitas Therapeutics, Inc. 190 Everett Ave Chelsea, MA 02150 USA
Protocol Version:	3.0
Version Date:	22-September-2015

-CONFIDENTIAL-

CIVITAS THERAPEUTICS PROTOCOL APPROVAL PAGE

[redacted]

Acorda Therapeutics, Inc., a duly authorized
signatory for Civitas Therapeutics, Inc.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Civitas Therapeutics.
- Not to implement any changes to the protocol without written agreement from Civitas Therapeutics and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Civitas Therapeutics including, but not limited to, the current Investigator's Brochure.
- That I am aware of, and will comply with, good clinical practice (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Civitas Therapeutics study drug and have been trained on their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____

Principal Investigator

LIST OF CONTACTS

Sponsor:	Civitas Therapeutics, Inc. 190 Everett Ave Chelsea, MA 02150 USA
Sponsor's Responsible Medical Director:	[redacted]
CRO Global Study Manager:	[redacted]
CRO Medical Monitors:	[redacted]
CRO Safety (Pharmacovigilance) Reporting:	[redacted]
Clinical Laboratory:	[redacted]
Spirometry and ECG Central Laboratory	[redacted]
DLco-Related Services and Analysis	[redacted]

	USA
Rater Training, Diary, and Endpoint Surveillance	[redacted]

2. SYNOPSIS

Title of Study:	A Phase 3, Randomized Study Investigating the Safety of CVT‑301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control
Protocol Number:	CVT-301-005
Investigators/Study Sites:	This study will be conducted at approximately 100 sites in Europe and the United States.
Phase of Development:	3
Objectives:	**Primary Objective** • To characterize the pulmonary safety, as assessed by spirometry (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/ FVC ratio), over a 12-month period within the CVT-301-treated patients. **Secondary Objectives** • To characterize the pulmonary safety, as assessed by spirometry (FEV1, FVC, and FEV1/FVC ratio), over a 12-month period in the observational ('standard of care') cohort. • To estimate the difference between the CVT-301-treated patients and the observational cohort on measures of pulmonary safety. • To characterize the effects of CVT-301 on safety over a 12-month period: safety will be assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS). • To evaluate the effect of CVT-301 on mean change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Q32-35] and wearing off [Q36-39]) measured pre-dose at 6 and 12 months after the initiation of CVT-301 treatment. • To characterize the occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic over a 12-month period • To describe the effects of CVT-301 on DLco over a 12-month period.

	Exploratory Efficacy Objectives • Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode. • Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively • Change from pre-dose in UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode. • Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11-point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes. • Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic, maintaining the ON state at 60 minutes after study drug administration (per the examiner's subjective assessment). • Patient-reported total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, assessed by the patient and recorded in the patient diary. • Change from baseline visit in the 39-Item Parkinson's Disease Questionnaire (PDQ-39). • Proportion of patients who improved based on the Patient Global Impression of Change (PGI-C) rating scale measured pre-dose. • Change from baseline visit in the Schwab and England (S&E) Activities of Daily Living (ADL) score. • Change from baseline visit UPDRS Part 2 score.
Study Design:	This study is a 12-month, open-label, randomized, multicenter study which will evaluate the safety and effects of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes) and will include a concurrent observational cohort of PD patients managed using the usual standards of care. Patients must be CVT-301-naïve, however, any patients that were enrolled from the CVT-301-002 and CVT-301-003 studies under the previous version of this protocol will be allowed to continue in the study. Patients will be randomized in a 2:1 ratio to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD FPD) or the observational cohort. Randomization will be differentiated by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%). Patients assigned to the CVT-301 treatment group may use the

	prescribed dose of CVT-301 as needed for the treatment of up to 5 OFF episodes per day in addition to their standard PD medications which may be modified as needed for symptomatic treatment over the 12-month study. Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode) to deliver the dose. Patients assigned to the observational cohort will not receive CVT-301 but will be permitted to be managed using their standard PD medications and other PD treatment modalities, which may be modified as needed for symptomatic treatment in accordance with usual practice over the 12-month study. For both the CVT-301 treatment group and the observational cohort, additions to and/or modification of the patient's usual PD treatment regimen may take place. However, oral "as-needed" (PRN) LD formulations are not permitted for CVT-301-treated subjects (refer to Section 9.4.2 of the protocol for a list of prohibited treatments and prohibited medications). For CVT-301-treated patients, the total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day. The study includes a screening period of up to 35 days (with 2 screening visits) and a treatment period of approximately 12 months (52±2 weeks) (with 6 treatment/observational visits) plus an additional follow-up at a pulmonary laboratory 4 to 5 weeks after the last treatment/observational visit. A longer screening period may be permitted with approval from the Sponsor. Planned treatment/observational visits will occur at 0 (pre-dose, baseline) and approximately 1, 3, 6, 9, and 12 months. For the CVT-301 treatment group these visits will be treatment visits, and for the observational cohort, these will be observational visits. All patients, regardless of study group, will be required to attend all of the screening visits and all of the treatment/observational visits. Assessments for DLco will be performed at a pulmonary laboratory outside of the clinic prior to the first treatment or observational visit, within 2 weeks prior to the 3-, 6-, 9-, and 12-month visits, and 4 to 5 weeks after Treatment Visit/Observational Visit 6 (TV/OV6). If a patient in the CVT-301 treatment group develops significant tolerability concerns that in the opinion of the investigator are of a severity that should necessitate a reduction in dose, including, but not limited to the exacerbation or worsening of troublesome dyskinesia, other problematic dopaminergic symptoms, or other tolerability concerns, a dose reduction from 2 capsules (50 mg LD FPD) to 1 capsule (25 mg LD FPD) per treated episode may be permitted. The medical monitor should be contacted, and the investigator should use his/her clinical judgment to determine whether an additional visit is required and what assessments should be performed (e.g., physical examination, spirometry, etc.). The patient should continue to use 1 capsule (25 mg LD FPD) per treated episode for a period of at least 1 week. If the investigator determines that the tolerability issue has adequately resolved and that the patient

	has tolerated this dose for at least 1 week, the patient may at that point either resume taking the original dose (2 capsules [50 mg LD FPD] per treated episode) or come into the clinic for an unscheduled visit to receive a reduced-dose study drug kit (35 mg LD FPD). Clinical staff will call the patient 1 to 2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has escalated back to the full dose (50 mg LD FPD per treated episode) has another tolerability concern that in the opinion of the investigator is of a severity that should necessitate a second reduction in dose, an unscheduled visit will be required and a reduced-dose study drug kit (35 mg LD FPD per treated episode) will be provided. He/she will remain on the reduced dose (35 mg LD FPD) for the remainder of the study; he/she will not be eligible for any additional up-titration in dose. Safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) that will include relevant medical experts asdefined in the DSMB Charter. Interim analyses, which will not affect study conduct, may be performed to support regulatory submissions. These analyses will be described in the SAP. **Screening Period** All patients will undergo a screening period of up to 35 days before entering the treatment period. The screening period may be extended an additional 7 days if repeat screening assessments are required. The screening period will consist of 2 scheduled clinic visits: Screening Visit 1 (SV1) and Screening Visit 2 (SV2). **Screening Visit 1 (SV1): Within 35 days prior to Treatment Visit/Observational Visit 1 (TV/OV1)** Patients will be instructed to bring all of their medications with them to SV1. Patients will provide written informed consent before any study procedures are performed. Patients will be assessed for eligibility based on the inclusion/exclusion criteria. The patient's medical history (including smoking history) and PD history will be documented. The PD diagnosis will be confirmed using Steps 1 and 2 of the United Kingdom (UK) Brain Bank Criteria, and the PD severity will be staged using the Hoehn and Yahr disease severity criteria. The number of hours of OFF time will be recorded. Eligible patients must have, by self-report, motor fluctuations with daily OFF time averaging at least 2 hours per day (not including early morning OFF time and which will require confirmation using the PD Diary over a period of 3 consecutive days). Each patient's PD medications, including standard LD-containing regimen (number of times per day that LD-containing medications are administered and the total daily LD dose will be recorded) and other concomitant medications will be recorded and reviewed to ensure that specified PD and other medications have been stabilized in accordance with protocol-defined criteria. The following assessments will then be performed: Mini Mental State Examination (MMSE) while patient is in an ON state; a full physical examination; review of pulmonary function and pulmonary history by completion of the Pulmonary

	Function Baseline Questionnaire; ECG; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); and spirometry for determination of FEV1, FVC, and the FEV1/FVC ratio (while the patient is in an ON state). Patients will undergo UPDRS Part 3 assessments while in an ON state, and training on self-recognition of ON and OFF states and rating assessments while in an ON state. Note: An "ON state" is defined as the time when medication is providing benefit with respect to mobility, slowness, and stiffness, and may or may not be providing complete alleviation of all PD symptoms. An "OFF state" is defined as the time when medication has worn off and is no longer providing benefit with respect to mobility, slowness, and stiffness. OFF episodes may be heralded by non-motor symptoms (e.g., pain, anxiety) prior to the appearance of motor symptoms. Patients will undergo standard home PD Diary training for self-rating of OFF states, ON states, and dyskinesia. Patients will be tested (in both ON and OFF states) for competence at self-rating and must be within 75% concordance with the ratings of the examiner (at least 3 out of 4 half-hour sessions over the course of 2 hours); if concordance is not reached, the observation period may be extended for an additional 2 hours to obtain agreement on at least 6 of 8 half-hour sessions. If needed, the same training and testing may be repeated at an unscheduled visit between SV1 and SV2 or at SV2. If patients return for an unscheduled visit between SV1 and SV2 for concordance training and testing, the visit must occur more than 3 days prior to SV2. If patients do not achieve 75% concordance by the end of SV2, they will be considered screen failures. Patients will be trained on the proper technique to prepare and use the inhaler system using sham (i.e., empty) capsules per the Instructions for Use (IFU) while in an ON state. Patients will undergo clinical laboratory tests (patients do not need to be in a fasted state, however, fasted status will be documented [fasting will be defined as at least 4 hours following the last meal or snack]) including serum pregnancy test for women of child-bearing potential. Patients will remain in the clinic and further PD medications will be withheld until they turn into an OFF state. The spirometry evaluations, UPDRS Part 3 assessments, patient training on self-report of ON/OFF states, and inhaler training should be repeated when patients are in an OFF state. Note: If a patient arrives at the clinic in an OFF state, these assessments will be done in an OFF state first, then they will be repeated in an ON state after the patient has taken his/her standard dose of PD medications and reverts to an ON state. The PD Diary (which will be used to record time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia, and time asleep) and the Screening ON/OFF Episodes Log (which will be used to record the discrete

	number of OFF episodes during their waking day) will be distributed to patients, and the instructions for completion will be reviewed. If needed, caregivers will also be trained on how to prepare inhalers for patients and how to complete the PD Diary and Screening ON/OFF Episodes Log. The next visit will be scheduled. Patients will be monitored for AEs throughout the visit. During the 3 consecutive days prior to SV2, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for SV2, the patients will take all of their usual prescribed non-PD medications and PD medications, including LD-containing PD medications. Clinic staff will arrange to speak with patients by telephone approximately 4 days prior to SV2 to confirm the next study visit and to remind patients of the study procedures required prior to the next scheduled study visit (including completion of the PD Diary and Screening ON/OFF Episodes Log). **Screening Visit 2 (SV2): At least 4 days after SV1** For the 3 consecutive days prior to SV2, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for SV2, the patient will take all of their usual prescribed non-PD medications and PD medications, including LD containing PD medications. At the clinic, the clinic staff will review the PD Diary and Screening ON/OFF Episodes Log to determine that patients are able to perform these procedures correctly and to determine eligibility. The staff will record any changes in the usual PD medication dose. Any changes in concomitant medications will be recorded. Patients will be trained again on the proper technique to prepare and use the inhaler system (using sham capsules) per the IFU. If the patient has undergone training on the inhaler in both the ON and OFF states at SV1, the inhaler training at SV2 may be done in either state. If not, the inhaler training at SV2 should be performed in both the ON and OFF states. Patients will be re-trained on how to self-assess their ON and OFF states while in ON and OFF states as needed. The clinic staff will distribute the PD Diary and the Screening ON/OFF Episodes Log and review the instructions for completion. The clinic staff will schedule patients to undergo a baseline DLco assessment, which will be completed after SV2 and before the first treatment or observational visit. The DLco assessment should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry. If needed, the following screening assessments performed at SV1 may be completed or repeated, if necessary, to verify or re-check results: MMSE (must be assessed in an ON state), full physical examination, ECG, standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR), spirometry (assessed in both ON and OFF states), UPDRS Part 3 (assessed in both ON and OFF

	states), ON/OFF concordance testing (assessed in both ON and OFF states), and clinical laboratory tests (with documentation of fasting status) including serum pregnancy test if applicable. Patients will be monitored for AEs throughout the visit. If a patient is unable to complete a screening assessment at SV2, an additional visit (repeat SV2) may be scheduled prior to randomization/treatment assignment. The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 4 to 6 days prior to TV/OV1 to confirm the DLco assessment has been done/scheduled, to confirm the next study visit, to remind patients of the study procedures required prior to the next scheduled study visit (including completion of the PD Diary and Screening ON/OFF Episodes Log). In addition, clinic staff will remind the patients during the call that they must be symptom-free of any flu-like syndrome or other respiratory infection for at least 3 days prior to TV/OV1 and that they should contact the site if an intervening illness occurs prior to TV/OV1. If a patient has any of these symptoms within this time period, the staff will reschedule this visit after these symptoms have been resolved for at least 3 days. The screening period may be extended for up to 2 weeks to accommodate this recovery. During the 3 consecutive days prior to TV/OV1, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for TV/OV1, patients will take all of their usual prescribed non-PD medications and PD medications, including LD-containing PD medications. **Randomization/Treatment Assignment** Following completion of SV2 and prior to randomization, the patients' eligibility criteria will be reviewed by delegated staff. Eligible patients will be randomized in a 2:1 ratio to the CVT-301 treatment group (CVT-301 50 mg PD FPD) or the observational cohort. Randomization will be differentiated by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each treatment group and by screening spirometry (FEV1 <60% of predicted *or* FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted *and* FEV1/FVC ratio ≥70%). Patients who previously completed the CVT-301-002 and CVT-301-003 studies will be assigned only to the CVT-301 treatment group. Sites must allow 7 business days between time of randomization and the first treatment visit (TV1) to allow time for drug to be shipped and received. **Treatment/Observational Period** Patients in both the CVT-301 treatment group and observational cohort are required to attend all of the in-clinic treatment/ observational visits. The assessments and procedures for the in-clinic treatment/observational visits will differ for patients in the CVT-301 treatment group compared to the observational cohort. All patients, regardless of treatment group, should continue with their usual prescribed standard PD medication regimen for the duration of

	the study which may be modified for symptomatic treatment during the study in accordance with usual practice. **Treatment Visit/Observational Visit 1 (TV/OV1): At least 7 days after SV2** Patients will complete the Screening ON/OFF Episodes Log and PD Diary for the 3 consecutive days prior to TV/OV1. Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of arrival for TV/OV1 should be scheduled to increase the likelihood that patients will be in the ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all of their usual PD medications. The clinic staff will collect the Screening ON/OFF Episodes Log and PD Diary, review the information, sign and date each, and confirm that the DLco assessment was performed prior to the visit (and if not, the study visit must be re-scheduled). Clinic staff will record the time patients took their usual PD medications prior to the visit and record any changes in standard PD medication dose/regimen. The following assessments will be performed: review of concomitant medications; PDQ-39 (in an ON state); brief physical examination; UPDRS Part 2 (preferably in the ON state); S&E ADL scale (preferably in the ON state); ECG; standard and orthostatic BP and HR; RR; spirometry (preferably in the ON state); clinical laboratory tests (with documentation of fasting status) including serum pregnancy test, if applicable; C-SSRS; Epworth Sleepiness Scale; and the QUIP. **In addition for the CVT-301 treated group only:** Clinic staff will distribute the Inhaled Dosing Log for recording the number of times the inhaler was used and the number of capsules used for each inhalation (to be completed daily throughout the 12-month treatment period). Clinic staff will distribute the PD Diary which will be used to record time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia, and time asleep (to be completed for the 3 consecutive days prior to the treatment visits). The UPDRS Part 4 (Questions 32-35 and 36-39) will be completed. The clinic staff will provide study drug kits. Patients will be trained again on the proper technique to prepare and use the inhaler system (using sham capsules) per the IFU. Under clinic staff supervision, preferably between 2 and 5 hours after receiving their previous dose of oral PD medications (in the OFF state), patients will prepare and self-administer their entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their

	prior oral PD medication. Vital signs (standard vital signs [BP and HR] and orthostatic vital signs [BP and HR]) will be assessed at 20 and 60 minutes post-dose. Respiratory rate will be assessed at 10, 20, 30, and 60 minutes post-dose. Patients will be monitored for AEs throughout the visit. Upon completion of the 60-minute observations, the patient's usual schedule of standard PD medications will be resumed for the remainder of the day (the patient may use the inhaled study drug up to 4 more times at home that day after he/she leaves the clinic, if needed for OFF episodes). Clinic staff will arrange to speak with patients by telephone 1 to 3 days after the visit to monitor for AEs and to discuss concerns or challenges with the inhaler systems or Inhaled Dosing Log. **All Patients:** The next study visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks before TV/OV2 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log (CVT arm only), to monitor for any AEs, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit (CVT arm only), and also to remind patients of the study procedures required prior to the next scheduled study visit (including completion of the PD Diary and applicable, the Inhaled Dosing Log). **At-Home Dosing for the CVT-301 Treatment Group** At TV/OV1, TV/OV2, TV/OV3, TV/OV4, and TV/OV5, patients in the CVT-301 treatment group will receive study drug kits and the IFU to take home with them. Patients will be instructed to take their standard oral PD medications as prescribed on their usual schedule of administration, which may be modified as needed for symptomatic treatment during the 12-month study. Additions to and/or modification of the patient's usual PD treatment regimen may take place. Oral PRN LD formulations are not permitted for these patients (refer to Section 9.4.2 of the protocol for a list of prohibited treatments and prohibited medications). The total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day. Patients will be instructed to administer inhaled study drug up to 5 times during the waking day *as close as possible to the time when they begin to experience OFF symptoms*. The PD symptomatology defining the onset of an OFF state may vary by patient, but typically is indicated by the return of PD motor symptoms such as tremor or bradykinesia; for some patients, OFF episodes may be heralded by non-motor symptoms (e.g., pain or anxiety) shortly prior to the appearance of motor symptoms. Study drug may **not** be used for the treatment of early morning OFF periods (i.e., morning akinesia). Patients may not take their inhaled study drug within 45 minutes following their previous dose of standard oral PD medication. These patients may not take oral PRN

	medications to manage OFF states during the study. In the event that an OFF state is not sufficiently resolved within 45 minutes of completing the last capsule inhalation, patients may resume their usual prescribed PD medication, if they have not already done so (i.e., according to their standard dose schedule/regimen); patients may not re-dose with inhaled study drug for that episode. If patients experience more than 5 OFF episodes per day that require treatment, they should adhere to their standard oral regimen for management of any additional OFF episodes; they may not treat these episodes with additional inhalations of study drug. Patients will complete the PD Diary for the 3 consecutive days prior to TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6. Patients will complete the Inhaled Dosing Log every day during the 12-month treatment period. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV/OV1 and 2 weeks (± 3 days) prior to each visit for TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6. They will bring the PD Diary, Inhaled Dosing Log, empty capsules, inhalers, and unused supplies to the each clinic visit. Unused supplies can be re-dispensed to the patient at each clinic visit, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed. If the patient begins to run low on study supplies in between treatment visits, they should contact the site. **Treatment Visit/Observational Visit 2 (TV/OV2): 1 month (4 weeks ±5 days) after TV/OV1** Patients will bring their usual PD medications and report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Clinic staff will record any changes in standard PD medication dose/regimen and record the time that patients took their usual PD medications prior to the visit. The following assessments will be performed: recording of any changes in concomitant medications; brief physical examination; spirometry (preferably in the ON state); standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR). **In addition for the CVT-301 treated group only:** Patients will complete the PD Diary for the 3 consecutive days prior to TV2 and the Inhaled Dosing Log daily throughout the treatment

	period. The clinic staff will review, sign, and date the PD Diary and Inhaled Dosing Log and collect all used and unused supplies. Unused supplies can be re-dispensed to the patient, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed. The staff will also review inhaler training, provide the PD Diary and Inhaled Dosing Log and review instructions for completion. Patients will be instructed to collect used empty capsules and return them at the next visit along with the PD Diary, Inhaled Dosing Log, and other study supplies. The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patients will undergo UPDRS Part 3 assessments, immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. Exploratory efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. Adverse events will be monitored throughout the visit. Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes). **All patients:** The next study visit will be scheduled. The clinic staff will schedule patients to undergo DLco at the pulmonary function lab, to occur within 2 weeks prior to the next study visit. The evaluation should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician). As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to TV/OV3 to address any potential concerns or challenges with the PD Diary, inhaler systems or Inhaled Dosing Log (CVT arm only), to monitor for any AEs, to confirm that the DLco assessment has been done/scheduled, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit (CVT arm only), and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and the Inhaled Dosing Log, as applicable).

	Treatment Visit/Observational Visit 3 (TV/OV3): 3 months (12±2 weeks) after TV/OV1 Patients will bring their usual PD medications and report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Clinic staff will confirm that the DLco assessment has been completed within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in standard PD medication dose/regimen and record the time that patients took their usual PD medications prior to the visit. The following assessments will be performed: recording of any changes in concomitant medications; C-SSRS; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; spirometry (preferably in the ON state); and clinical laboratory tests (with documentation of fasting status) including serum pregnancy test, if applicable. **In addition for the CVT-301 treated group only:** Patients will complete the PD Diary for the 3 consecutive days prior to TV3 and the Inhaled Dosing Log daily throughout the treatment period. The clinic staff will review, sign, and date the PD Diary and Inhaled Dosing Log and collect all used and unused supplies. Unused supplies can be re-dispensed to the patient, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed. The staff will also review inhaler training, provide the PD Diary and Inhaled Dosing Log and review instructions for completion. Patients will be instructed to collect used empty capsules and return them at the next visit along with the PD Diary, Inhaled Dosing Log, and other study supplies. The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will undergo UPDRS Part 3 assessments, immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. Exploratory efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose;

	(2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. The PGI-C will be completed, preferably in the ON state and must be done before other study evaluations. Adverse events will be monitored throughout the visit. Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes). **All patients:** The next study visit will be scheduled. The clinic staff will schedule patients to undergo DLco at the pulmonary function lab, to occur within 2 weeks prior to the next study visit. The evaluation should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician). As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to TV/OV4 to address any potential concerns or challenges with the PD Diary, inhaler systems or Inhaled Dosing Log (CVT arm only), to monitor for any AEs, to confirm that the DLco assessment has been done/scheduled, to confirm their next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and the Inhaled Dosing Log, as applicable). **Treatment Visit/Observational Visit 4 (TV/OV4): 6 months (24±2 weeks) after TV/OV1** Patients will bring their usual PD medications and report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). They will confirm that the DLco assessment has been completed within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in standard PD medication dose/regimen and record the time that patients took their usual PD medications prior to the visit. The following assessments will be performed: recording of any changes in concomitant medications; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; spirometry (preferably in the ON state); and clinical laboratory tests

	(with documentation of fasting status) including serum pregnancy test, if applicable. In addition the following assessments will be recorded: the PDQ-39, UPDRS Part 2, and S&E ADL scale (each preferably in the ON state); QUIP; Epworth Sleepiness Scale; and C-SSRS. **In addition for the CVT-301 treated group only:** Patients will complete the PD Diary for the 3 consecutive days prior to TV4 and the Inhaled Dosing Log daily throughout the treatment period. The clinic staff will review, sign, and date the PD Diary and Inhaled Dosing Log and collect all used and unused supplies. Unused supplies can be re-dispensed to the patient, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed. The staff will also review inhaler training, provide the PD Diary and Inhaled Dosing Log and review instructions for completion. Patients will be instructed to collect used empty capsules and return them at the next visit along with the PD Diary, Inhaled Dosing Log, and other study supplies. The UPDRS Part 4 (Questions 32-35 and 36-39) will be completed The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will undergo UPDRS Part 3 assessments, immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. Exploratory efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. The PGI-C will be completed, preferably in the ON state and must be done before other study evaluations. Adverse events will be monitored throughout the visit. Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes). **All patients:** The next study visit will be scheduled. The clinic staff will schedule patients to undergo DLco at the pulmonary function lab, to occur within 2 weeks prior to the next study visit. The evaluation should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician). As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

	Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to TV/OV5 to address any potential concerns or challenges with the PD Diary, inhaler systems or Inhaled Dosing Log (CVT arm only), to monitor for any AEs, to confirm that the DLco and spirometry assessments has been done/scheduled, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and the Inhaled Dosing Log, as applicable). **Treatment Visit/Observational Visit 5 (TV/OV5): 9 months (36±2 weeks) after TV/OV1** Patients will bring their usual PD medications and report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Clinic staff will confirm that the DLco assessment has been completed within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in standard PD medication dose/regimen and record the time that patients took their usual PD medications prior to the visit. The following assessments will be performed: recording of any changes in concomitant medications; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); spirometry (preferably in the ON state); clinical laboratory tests (with documentation of fasting status) including serum pregnancy test, if applicable; and the C-SSRS assessment. **In addition for the CVT-301 treated group only:** Patients will complete the PD Diary for the 3 consecutive days prior to TV5 and the Inhaled Dosing Log daily throughout the treatment period. The clinic staff will review, sign, and date the PD Diary and Inhaled Dosing Log and will collect all used and unused supplies. Unused supplies can be re-dispensed to the patient, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed. The staff will also review inhaler training, provide the PD Diary and Inhaled Dosing Log and review instructions for completion. Patients will be instructed to collect used empty capsules and return them at the next visit along with the PD Diary, Inhaled Dosing Log, and other study supplies. The patient will remain in the clinic until he/she goes into the OFF

	state. In the OFF state, the patient will undergo UPDRS Part 3 assessments, immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. The clinic staff will assess: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. Adverse events will be monitored throughout the visit. Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes). **All patients:** The next study visit will be scheduled. The clinic staff will schedule patients to undergo DLco at the pulmonary function lab, to occur within 2 weeks prior to the next study visit. The evaluation should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician). As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to TV/OV6 to address any potential concerns or challenges with the PD Diary, inhaler systems or Inhaled Dosing Log (CVT arm only), to monitor for any AEs, to confirm that the DLco and spirometry assessment has been done/scheduled, to confirm their next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and as applicable, the Inhaled Dosing Log). **Treatment Visit/Observational Visit 6 (TV/OV6) / Early Withdrawal Visit:12 months (52±2 weeks) after TV/OV1** Patients will bring their usual PD medications and report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home).

	Clinic staff will confirm that DLco assessment was performed within 2 weeks prior to the visit (and if not, re-schedule study visit). Clinic staff will record any changes in standard PD medication dose/regimen and record the time that patients took their usual PD medications prior to the visit. The following assessments will be performed: recording of any changes in concomitant medications; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; spirometry (preferably in the ON state); and clinical laboratory tests (with documentation of fasting status) including serum pregnancy test, if applicable. In addition the following assessments will be recorded: the PDQ-39, UPDRS Part 2, and S&E ADL scale (each preferably in the ON state); QUIP; Epworth Sleepiness Scale; and C-SSRS. **In addition for the CVT-301 treated group only:** Patients will complete the PD Diary for the 3 consecutive days prior to TV6 and the Inhaled Dosing Log daily throughout the treatment period. The clinic staff will review, sign, and date the PD Diary and Inhaled Dosing Log and collect all used and unused supplies. The UPDRS Part 4 (Questions 32-35 and 36-39) will be completed The patient will remain in the clinic until he/she goes into the OFF state. Patients will be provided with a new inhaler for dosing at TV/OV6 and will use study drug from the supplies brought to the visit. In the OFF state, the patient will undergo UPDRS Part 3 assessments, immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. Exploratory efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. The PGI-C will be completed, preferably in the ON state and must be done before other study evaluations. **All patients:** Adverse events will be monitored throughout the visit. Once all of the assessments are complete, patients will be scheduled for a DLco assessment 4 to 5 weeks after TV/OV6. The DLco assessment should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry. Patients who withdraw prematurely will complete the TV/OV6 assessments at the time of withdrawal (except the pre-TV/OV6 DLco assessment) and will be scheduled to undergo a DLco

	assessment 4 to 5 weeks after TV/OV6.
Selection of Patients:	All patients must meet the inclusion criteria and must not meet any of the exclusion criteria to be eligible for this study. Patients previously enrolled in the CVT-301-002 and CVT-301-003 studies must have completed all of the CVT-301 study visits without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from either of the CVT-301 studies prior to completion, *for any reason*, will not be eligible. **Inclusion Criteria:** • Has signed and dated an IRB/IEC-approved informed consent form before any protocol-specific screening procedures are performed. • Is a male or female aged 30 to 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study. • Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the UK Brain Bank criteria, diagnosed after the age of 30 years. • Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity. • Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period. • Patients who are on a LD-containing therapy, not including Rytary (or equivalent), must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/dopamine decarboxylase inhibitor (DDI)-containing regimen. • Patients who are on a LD containing therapy, when including Rytary (or equivalent), should be on a stable dose for at least 6 weeks prior to SV1 • The frequency of L-dopa administrations must be at least 3 times during the waking day and a total daily LD dose of ≤1600 mg (exclusive of PRN LD-containing medications). • Patients should be stable on other PD medications for at least 4 weeks prior to SV1. • Patients must have a ≥25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening. • Patients must have normal cognition as confirmed by a score

	of ≥25 on the MMSE, performed in the ON state. • Patients must be able to perform a spirometry maneuver in the ON and OFF states, and must have a screening FEV1 ≥50% of predicted and an FEV1/FVC ratio >60% in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine potential eligibility. All CVT-301-naïve patients with an FEV1/FVC ratio of >60% to <70% will be required to undergo a bronchodilator challenge and the results must be reviewed prior to entry into the study. Patients with an FEV1/FVC ratio that is >60% to <70% will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/European Respiratory Society [ERS] criteria prior to randomization. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization.) **Exclusion Criteria:** • Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures. • Pregnant or lactating females or females wishing to become pregnant. • Patients who have any known contraindication to the use of LD, including a history of malignant melanoma or a history of narrow-angle glaucoma. • Patients who have had previous surgery for PD (including but not limited to deep brain stimulation [DBS] or cell transplantation). • Patients with a history of psychotic symptoms requiring treatment, or suicide ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of anti-depressant and certain low-dose atypical antipsychotic medications are permitted, in case they are indicated to treat symptoms other than psychotic symptoms). • Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years. • Patients taking certain prohibited medications (see Section 9.4.2). • Patients with a history of drug or alcohol abuse within the prior 12 months.

	• Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years. • Patients with any contraindication to performing routine spirometry or who are unable to perform a spirometry maneuver (see Appendix 20 for a list of contraindications). • Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment. • Patients with any condition that in the investigator's opinion would make patients unsuitable or interfere with their participation in the study. Potential issues of concern should be raised to the medical monitor during eligibility review. • Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety. • Patients who have been treated with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the beginning of the screening period (this includes investigational formulations of marketed products). • Prior exposure to CVT-301.
Planned Sample Size:	Approximately 250 CVT-301 treatment patients and 115 control patients will be enrolled in this study. It is assumed that the drop-out rate will be approximately 25%.
Investigational Therapy (for the CVT-301 treatment group):	**CVT-301 (levodopa inhalation powder [LIP])** Each dose will be administered using 2 sequential inhalations of CVT-301-filled capsules. CVT-301 capsules will be delivered using the CVT-301 inhalers. [redacted] The capsules provided to the CVT-301 treatment group (target nominal respirable dose of approximately 50 mg LD FPD) will deliver approximately 25 mg LD FPD to the lung per capsule inhalation.
Reference Therapy:	There will be no reference therapy or placebo. Patients in both the CVT-301 treatment group and the observational cohort will be managed with their standard PD treatment throughout the study; modification of the standard PD treatment is permissible, as outlined in this protocol.
Treatment Duration:	The planned treatment period will be 52 ±2 weeks. Each patient in the CVT-301 treatment group will self-administer up to 5 doses of inhaled study drug per day. The maximum planned screening period is approximately 5 weeks. A follow-up pulmonary evaluation will occur at 4 to 5 weeks after the treatment period ends.
Criteria for Evaluation:	**Safety** Pulmonary safety will be evaluated from assessments of lung

	function, as measured from spirometry (FEV1, FVC, FEV1/FVC ratio). In addition, DLco will be evaluated. Safety will also be assessed from physical examinations, AE reports, standard and orthostatic vital signs (BP, HR, and RR), clinical laboratory values (hematology and biochemistry), ECGs, the QUIP, Epworth Sleepiness Scale, the C-SSRS, UPDRS Part 4 (Questions 32-35 and 36-39), and occurrence and severity of examiner-rated dyskinesia after study drug is administered in the clinic. **Exploratory Efficacy** • UPDRS Part 3 motor score, assessed pre-dose and at 10, 20, 30, and 60 minutes following treatment in the clinic. Occurrence of an ON state during the 60-minute post-dose period and if an ON state occurs during the 60-minute post-dose, whether or not the patient is still in the ON state at 60 minutes post-dose. • Occurrence of an ON state during the 60-minute post-dose period and if an ON state occurs during the 60-minute post-dose, whether or not the patient is still in the ON state at 60 minutes post-dose • PD diary information on total daily ON time without dyskinesia, total daily ON time with troublesome dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily OFF time for the 3 consecutive days prior to each treatment visit • PDQ-39 • PGI-C • S&E ADL • UPDRS Part 2
Statistical Methods and Planned Analyses:	For all statistical analyses of the CVT-301 treatment group, the visit at which the CVT-301 treatment was initiated will be used as the baseline. However, for all enrolled patients who were previously included in the CVT-301-002 or CVT-301-003 studies, TV/OV1 of the CVT-301-005 study will be used as baseline. For the observational cohort, the assessments at TV/OV1 will be used as baseline. All patients who are enrolled in CVT-301-005 and receive at least 1 dose of CVT-301 will be included in the safety and exploratory endpoint analyses. Patients in the observational cohort will be included in the analyses if they provide any data after TV/OV1. **Safety Analyses** The extent of exposure to study treatment will be summarized for the patients who received CVT-301 treatment. The time period between TV/OV1 and TV/OV6 (or Early Withdrawal Visit) will be used as the measure of extent of exposure for patients randomized to the observational cohort. Adverse events will be tabulated by treatment group according to the Medical Dictionary for Regulatory Activities (MedDRA). Study-emergent and treatment-emergent adverse events

	(TEAEs) will be summarized by body system and preferred term. For patients in the observational cohort, the AEs collected between TV/OV1 and TV/OV6 (or Early Withdrawal Visit) will be considered as TEAEs. Furthermore, the time of onset of the TEAEs will be summarized. For vital signs, ECG parameters, spirometry measurements, and DLco, the changes from pre-dose to post-dose assessments of the corresponding day will be calculated and described using descriptive statistics. For spirometry, DLco, and safety laboratory variables, the differences in pre-dose values between the study days will be described. Furthermore, the changes in the spirometry values and difference between the groups will be estimated using a Mixed Model for Repeated Measurements (MMRM) similar to the one used for the exploratory endpoint variables. The proportion of patients with abnormal spirometry values will be tabulated using different criteria for the threshold (e.g., at least 10% or 20% change from baseline at any single visit, at least 10% or 20% change from baseline on at least 2 consecutive visits). The proportions of patients meeting ATS quality criteria (and also for those 'rejected') will be summarized. All spirometry analyses will be performed both for all patients regardless of the ATS quality criteria and separately excluding the assessments not meeting the ATS quality criteria. Changes from baseline to follow-up in the rating scales for assessing suicidality, somnolence, and impulse control disorders will be summarized descriptively. Demographics and baseline characteristics will be summarized descriptively. **Exploratory Endpoint Analyses** The objectives related to the exploratory endpoints will primarily be assessed for the CVT-301-treated patients. The same objectives will be explored for the pool of CVT-301 naïve patients and patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies, if feasible. The changes from baseline in continuous exploratory endpoint variables will be estimated using an MMRM. The model will include visit and the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) as fixed factors. The baseline value will be used as a covariate.. The categorical data will be primarily evaluated descriptively. Each visit will be evaluated separately for the categorical endpoints. The exploratory endpoint data collected from the patients in the observational cohort will be summarized with descriptive statistics.

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LIST OF IN-TEXT TABLES

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4. LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	adverse event
ANCOVA	analysis of covariance
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
BP	blood pressure
CD	carbidopa
CD/LD	carbidopa/levodopa
CFR	Code of Federal Regulations
C_{max}	maximal plasma concentration
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DDI	dopamine decarboxylase inhibitor
DPPC	dipalmitoyl phosphatidylcholine
DBP	diastolic blood pressure
DBS	deep brain stimulation
DLco	carbon monoxide diffusing capacity
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ERS	European Respiratory Society
FEV1	forced expiratory volume in 1 second
FPD	fine particle dose (i.e., pulmonary-delivered dose)
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	good clinical practice
GI	gastrointestinal
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996

HPMC	hydroxypropyl methylcellulose
HR	heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IND	Investigational New Drug
IRB	Institutional Review Board
LD	levodopa
LIP	levodopa inhalation powder (CVT-301)
MAO-B	monoamine oxidase-B
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters mercury
MMRM	Mixed Model for Repeated Measurements
MMSE	Mini Mental State Examination
NaCl	sodium chloride
NHANES III	Third National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
PD	Parkinson's disease
PDQ-39	39-Item Parkinson's Disease Questionnaire
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic
PRN	as needed
QUIP	Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire
RR	respiratory rate
S&E	Schwab and England
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SV1	Screening Visit 1
SV2	Screening Visit 2
T0	time of completion of inhalation of the last capsule of inhaled study treatment administered
t_{max}	time to maximal drug concentration
TEAE	treatment-emergent adverse event

TV/OV1	Treatment Visit/Observational Visit 1
TV/OV2	Treatment Visit/Observational Visit 2
TV/OV3	Treatment Visit/Observational Visit 3
TV/OV4	Treatment Visit/Observational Visit 4
TV/OV5	Treatment Visit/Observational Visit 5
TV/OV6	Treatment Visit/Observational Visit 6
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
USA	United States of America

5. INTRODUCTION

5.1. Background and Rationale

5.1.1. Background on Motor Fluctuations in Parkinson's Disease Patients

Levodopa (LD) remains the "standard of care" for the management of motor symptoms for Parkinson's disease (PD) patients. However, long-term treatment with LD is complicated by the development of motor fluctuations, also referred to as hypomobility or OFF episodes. The development of OFF episodes relates to both pharmacokinetic (PK) and pharmacodynamic factors. Over time, patients frequently experience a progressive shortening of the duration of LD clinical effect, leaving patients vulnerable to episodic OFF episodes which may be disabling. It is estimated that up to half of LD-treated PD patients develop such motor fluctuations within 5 years (Parkinson Study Group 1996, LeWitt 2008, Stocchi 2010).

Following oral ingestion, LD is absorbed through an active transport mechanism that is specific for large neutral L-amino acids in the proximal small intestine. The absorption of LD is subject to considerable inter- and intra-patient variability and is affected significantly by alterations in gastrointestinal (GI) motility and food intake. Frequently, poor absorption following administration of a standard oral LD dose results in sub-therapeutic levels, leaving patients susceptible to the development of OFF episodes (Baruzzi 1987, Pfeiffer 1996, Olanow 2006).

Treatment options for patients with motor response fluctuations are limited. Various strategies may be employed to enhance the clinical effectiveness of central dopaminergic stimulation to reduce the frequency of motor fluctuations, including the use of dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, extended-release oral LD formulations, or modified dosage of their standard oral LD preparations (LeWitt 2008, Olanow 2009).

Management of OFF episodes is done frequently through adjustment of the inter-dose interval of standard oral LD preparations or through administration of unscheduled partial or full doses of oral LD-containing products. However, following treatment with oral LD preparations, resumption of motor function is unreliable owing to the challenges in GI transit and LD absorption (Ondo 2010), and the development of intermittent OFF episodes remains a significant issue despite attempts to manage patients using oral LD agents alone.

[redacted] CVT-301 (LD inhalation powder) is being developed for the treatment of episodic motor fluctuations (OFF episodes) in patients with PD, as an adjunct, as needed (PRN) therapy to provide relief from intermittent motor fluctuations (OFF episodes) that affect many PD patients.

5.1.2. Background on CVT-301 (Levodopa Inhalation Powder)

CVT-301 is a dry powder LD formulation (levodopa inhalation powder [LIP]) designed for inhaled delivery using a proprietary delivery system. Using this technology, a variety of medications have been administered previously to humans, including proteins (e.g., insulin, human growth hormone) and small molecules (e.g., epinephrine, trospium) (Rave 2007,

Chipman 2005, Walvoord 2009, Dewey 2001, Dunbar 2004, Oleson 2010). This delivery system is capable of delivering therapeutics with high efficiency over a range of inspiratory flow rates using a passive, breath-actuated device (DeLong 2005).

CVT-301 is being developed as treatment for episodic motor fluctuations (OFF episodes) in patients with PD. CVT-301 will be used as an adjunct to the patient's existing decarboxylase inhibitor (i.e., carbidopa [CD] or benserazide)-inclusive PD medication regimen.

In nonclinical studies, CVT-301 pulmonary delivery was associated with rapid LD absorption, and was associated with a shorter and less variable time to maximal drug concentration (tmax) and less variable maximal plasma concentration (Cmax) compared to oral LD administration. These PK attributes translated to pharmacodynamic advantages in a nonclinical model of PD (Bartus 2004).

[redacted]

5.2. Rationale

Attainment of therapeutic plasma concentrations and restoration of motor function following administration of oral LD to PD patients is variable, unreliable, and frequently delayed, not uncommonly requiring 1 hour or more to attain therapeutic responses. [redacted]

The more rapid LD absorption following inhaled CVT-301 administration is expected to translate to rapid alleviation of motor OFF symptoms in patients experiencing OFF episodes.

This 12-month study will employ a randomized open-label methodology to investigate the safety and effects of CVT-301 (50 mg LD FPD) and will include a concurrent observational cohort of PD patients who will not receive study medication, but will continue to take their usual PD medications. Patients must be CVT-301-naïve, however, any patients that were enrolled from the CVT-301-002 and CVT-301-003 studies under the previous version of this protocol will be allowed to continue in the study Patients will be randomized in a 2:1 ratio to the CVT-301 treatment group (50 mg LD FPD) or the observational cohort.

During the 12-month treatment period, patients in the CVT-301 treatment group will self-administer an inhaled study drug dose as needed when they experience OFF episodes; study medication may be used up to 5 times daily. Every day during the treatment period, the CVT-301 patients will record the following information in the Inhaled Dosing Log: the number of times the inhaler was used and the number of capsules used for each inhalation treatment. Patients in each group will continue their standard PD medications, which may be modified during the study if needed. Patients in each group will be required to attend the screening visits (Screening Visit 1 [SV1] and Screening Visit 2 [SV2]) and the 6 in-clinic treatment/observational visits (Treatment Visit/Observational Visit 1 [TV/OV1], Treatment Visit/Observational Visit 2 [TV/OV2], Treatment Visit/Observational Visit 3 [TV/OV3], and Treatment Visit/Observational Visit 4 [TV/OV4], Treatment Visit/Observational Visit 5 [TVOV5], and Treatment Visit/Observational Visit 6 [TV/OV6]). For the patients in the CVT-301 treatment group, these visits will be treatment visits and for the observational cohort, these visits will be observational visits.

CVT-301-treated patients will be followed in the clinic for the following efficacy measures: serial assessments of UPDRS Part 3 motor score following treatment in the clinic, the occurrence and severity of dyskinesia following treatment in the clinic, the occurrence of ON states during the post-treatment period, the 39-Item Parkinson's Disease Questionnaire (PDQ-39), the Patient Global Impression of Change (PGI-C) rating scale, the Schwab and England (S&E) Activities of Daily Living (ADL) score; UPDRS Part 2 score, and UPDRS Part 4 (Questions 32-35 and 36-39) score. In addition, the total daily ON time without dyskinesia, total daily ON time with troublesome dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily OFF time will be evaluated in the CVT-301-treated patients based on the PD Diary, which will be completed for the 3 consecutive days prior to SV2, TV/OV1, TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6.

All patients, regardless of treatment assignment, will undergo the safety assessments. Patient safety will be evaluated using adverse event (AE) reports, physical examination, vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), spirometry, carbon monoxide diffusing capacity (DLco) maneuver, the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

The use of a randomized observational cohort in this study is to permit long-term contemporaneous temporal comparison to CVT-301-treated patients to describe any potential effects of CVT-301 with respect to lung function measurements. These control patients, who are eligible to use any approved treatments to manage their PD motor symptoms, represent a randomized study population that remains naïve to inhalation treatment (to avoid potential confounding interpretation of lung function data) for their PD which is required to ascertain the underlying variability in spirometry and DLco endpoints. Only a limited number of efficacy assessments will be evaluated in the patients randomized to the observational cohort. Selected efficacy measures to assess effects of CVT-301 will be evaluated in the open-label CVT-301-treated patients who use CVT-301 inhalation as a treatment of OFF symptoms.

5.2.1. Rationale for Selection of Dose

Because CVT-301 contains LD only (i.e., with no DDI), study drug will be administered only to patients taking a DDI-containing LD formulation (e.g., CD or benserazide). The study is designed to evaluate the safety and effect of adjunctive therapy (CVT-301 plus usual prescribed standard PD medication regimen). All patients, regardless of treatment assignment, will continue with their usual prescribed standard PD medication regimen for the study duration.

The dose level being studied has been observed to be clinically effective, safe, and tolerated in healthy adult volunteers as well as in PD patients in 2 completed CVT-301 clinical studies.

The PK data from the selected CVT-301 dose level (50 mg LD FPD) has been well-characterized from healthy adult volunteers in

CVT-301 (Levodopa Inhalation Powder)

The dose level of 50 mg LD FPD was selected for further evaluation in this study.

6. STUDY OBJECTIVES

Primary Objective

- To characterize the pulmonary safety, as assessed by spirometry (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/ FVC ratio), over a 12-month period within the CVT-301-treated patients.

Secondary Objectives

- To characterize the pulmonary safety, as assessed by spirometry (FEV1, FVC, and FEV1/FVC ratio), over a 12-month period in the observational ('standard of care') cohort.
- To estimate the difference between the CVT-301-patients and the observational cohort on measures of pulmonary safety.
- To characterize the effects of CVT-301 on safety over a 12-month period: safety will be assessed by AE reports, physical examination, standard and orthostatic vital signs (BP, HR, and RR), clinical laboratory tests, 12-lead ECGs, QUIP, the Epworth Sleepiness Scale, and the C-SSRS.
- To evaluate the effect of CVT-301 on mean change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Q32-35] and wearing off [Q36-39]) measured pre-dose at 6 and 12 months after the initiation of CVT-301 treatment.
- To characterize the occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic over a 12-month period.
- To describe the effects of CVT-301 on DLco over a 12-month period.

Exploratory Efficacy Objectives

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode.
- Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively

- Change from pre-dose in UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode.
- Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11-point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes.
- Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic, maintaining the ON state at 60 minutes after study drug administration (per the examiner's subjective assessment).
- Patient-reported total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, assessed by the patient and recorded in the patient diary.
- Change from baseline visit in the 39-Item Parkinson's Disease Questionnaire (PDQ-39).
- Proportion of patients who improved based on the Patient Global Impression of Change (PGI-C) rating scale measured pre-dose.
- Change from baseline visit in the Schwab and England (S&E) Activities of Daily Living (ADL) score.
- Change from baseline visit in the UPDRS Part 2 score.

7. INVESTIGATIONAL PLAN

This study is a 12-month, open-label, randomized, multicenter study which will evaluate the safety and effects of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes) and will include a concurrent observational cohort of PD patients managed using the usual standards of care. Patients must be CVT-301-naïve, however, any patients that were enrolled from the CVT-301-002 and CVT-301-003 studies under the previous version of this protocol will be allowed to continue in the study. Patients will be randomized in a 2:1 ratio to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD FPD) or the observational cohort. Randomization will be differentiated by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each group and by screening spirometry (FEV1 <60% of predicted *or* FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted *and* FEV1/FVC ratio ≥70%).

Patients assigned to the CVT-301 treatment group may use the prescribed dose of CVT-301 as needed for the treatment of up to 5 OFF episodes per day in addition to their standard PD medications which may be modified as needed for symptomatic treatment over the 12-month study. Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode) to deliver the dose.

Patients assigned to the observational cohort will not receive CVT-301 but will be permitted to be managed using their standard PD medications and other PD treatment modalities, which may be modified as needed for symptomatic treatment in accordance with usual practice over the 12-month study.

For both the CVT-301 treatment group and the observational cohort, additions to and/or modification of the patient's usual PD treatment regimen may include any PD treatments that are currently approved in the patient's region. However, oral PRN LD formulations are not permitted for CVT-301-treated subjects (refer to Section 9.4.2 for a list of prohibited treatments and prohibited medications). For CVT-301-treated patients, the total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day.

The study includes a screening period of up to 35 days (with 2 screening visits) and a treatment period of approximately 12 months (52±2 weeks) (with 6 treatment/observational visits) plus an additional follow-up at a pulmonary laboratory 4 to 5 weeks after the last treatment/observational visit. A longer screening period may be permitted with approval from the Sponsor. Planned treatment/observational visits will occur at 0 (pre-dose, baseline) and approximately 1, 3, 6, 9, and 12 months. For the CVT-301 treatment group, these visits will be treatment visits and for the observational cohort, these will be observational visits. All patients, regardless of treatment group, will be required to attend all of the screening visits and all of the treatment/observational visits. Assessments for DLco will be performed at a pulmonary laboratory outside of the clinic prior to the TV/OV1, within 2 weeks prior to the 3-, 6-, 9-, and 12-month visits, and 4 to 5 weeks after TV/OV6.

If a patient in the CVT-301 treatment group develops significant tolerability concerns that in the opinion of the investigator are of a severity that should necessitate a reduction in dose, including, but not limited to the exacerbation or worsening of troublesome dyskinesia, other problematic dopaminergic symptoms, or other tolerability concerns, a dose reduction from 2 capsules (50 mg LD FPD) to 1 capsule (25 mg LD FPD) per treated episode may be permitted. The medical monitor should be contacted, and the investigator should use his/her clinical judgment to determine whether an additional visit is required and what assessments should be performed (e.g., physical examination, spirometry, etc.). The patient should continue to use 1 capsule (25 mg LD FPD) per treated episode for a period of at least 1 week. If the investigator determines that the tolerability issue has adequately resolved and that the patient has tolerated this dose for at least 1 week, the patient may at that point either resume taking the original dose (2 capsules [50 mg LD FPD] per treated episode) or come into the clinic for an unscheduled visit to receive a reduced-dose study drug kit (35 mg LD FPD). Clinical staff will call the patient 1 to 2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has escalated back to the full dose (50 mg LD FPD per treated episode) has another tolerability concern that in the opinion of the investigator is of a severity that should necessitate a second reduction in dose, an unscheduled visit will be required and a reduced-dose study drug kit (35 mg LD FPD per treated episode) will be provided. He/she will remain on the reduced dose (35 mg LD FPD) for the remainder of the study; he/she will not be eligible for any additional up-titration in dose.

Safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) that will include relevant medical experts (including a neurologist and pulmonologist), an independent statistician, and additional representatives (as will be defined in the DSMB Charter). Safety data, including but not limited to AEs, spirometry, vital signs, and ECG data will be reviewed. The safety review will be documented in a DSMB Charter prior to the start of the study. In the event that potential safety issues are identified, the committee may recommend modification of the study design or study termination, which will be communicated promptly with investigators,

Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), and regulatory agencies, in accordance with legal and regulatory requirements.

An overview of the study visit schedule is presented in Appendix 1. Details on the assessments and procedures performed at each visit are presented in Appendix 2 through Appendix 15 and in Section 10.

8. STUDY POPULATION

All patients must meet the inclusion criteria and must not meet any of the exclusion criteria to be eligible for this study. Patients previously enrolled in the CVT-301-002 and CVT-301-003 studies must have completed all of the CVT-301 study visits without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from either of the CVT-301 studies prior to completion, *for any reason*, will not be eligible.

8.1. Inclusion Criteria

In order to be eligible to enter the study, patients must meet all of the following criteria:

1. Has signed and dated an IRB/IEC-approved informed consent form before any protocol-specific screening procedures are performed.
2. Is a male or female aged 30 to 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
3. Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the United Kingdom (UK) Brain Bank criteria, diagnosed after the age of 30 years.
4. Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
5. Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.

6a. Patients who are on a LD-containing therapy, not including Rytary (or equivalent), must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/DDI-containing regimen

6b. Patients who are on a LD-containing therapy, when including Rytary (or equivalent), should be on a stable dose for at least 6 weeks prior to SV1.

6c. The frequency of L-dopa administrations must be at least 3 times during the waking day and a total daily LD dose of ≤ 1600 mg.

7. Patients should be stable on other PD medications for at least 4 weeks prior to SV1.

8. Patients must have a ≥25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.
9. Patients must have normal cognition as confirmed by a score of ≥25 on the Mini Mental State Examination (MMSE), performed in the ON state.
10. 10. Patients must be able to perform a spirometry maneuver in the ON and OFF states, and must have a screening FEV1 ≥50% of predicted and an FEV1/FVC ratio >60% in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine potential eligibility. All CVT-301-naïve patients with an FEV1/FVC ratio that is >60% to <70% will be required to undergo a bronchodilator challenge and the results must be reviewed prior to entry into the study. Patients with an FEV1/FVC ratio that is >60% to <70% will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/European Respiratory Society [ERS] criteria prior to randomization. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization.)

8.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria at screening will not be enrolled in the study:

1. Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures.
2. Pregnant or lactating females or females wishing to become pregnant.
3. Patients who have any known contraindication to the use of LD, including a history of malignant melanoma or a history of narrow-angle glaucoma.
4. Patients who have had previous surgery for PD (including but not limited to deep brain stimulation [DBS] or cell transplantation).
5. Patients with a history of psychotic symptoms requiring treatment, or suicide ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of anti-depressant and certain low-dose atypical antipsychotic medications are permitted in case they are indicated to treat symptoms other than psychotic symptoms).
6. Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
7. Patients taking certain prohibited medications (see Section 9.4.2).
8. Patients with a history of drug or alcohol abuse within the prior 12 months.
9. Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years.

10. Patients with any contraindication to performing routine spirometry or who are unable to perform a spirometry maneuver (see Appendix 20 for a list of contraindications).
11. Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment.
12. Patients with any condition that in the investigator's opinion would make patients unsuitable or interfere with their participation in the study. Potential issues of concern should be raised to the medical monitor during eligibility review.
13. Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety.
14. Patients who have been treated with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the beginning of the screening period (this includes investigational formulations of marketed products).
15. Prior exposure to CVT-301.

Note: An active or recent (within 3 days) respiratory infection will not disqualify a patient from enrolling in the study. However, all symptoms should be resolved for at least 3 days prior to the baseline visit (TV/OV1) (the screening period may be extended for up to 2 weeks to accommodate this recovery).

8.3. Removal of Patients from Study

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. If a patient is discontinued prematurely at any time after entering the study, the investigator will make every effort to see the patient and complete the TV/OV6 assessments as shown Appendix 14 (for patients in the CVT-301 treatment group) or Appendix 15 (for patients in the observational cohort). If a patient is withdrawn due to an AE, the event must be followed, when possible, until resolution.

An end-of-study page in the electronic case report form (eCRF) should be completed for every patient who receives study drug (if in the CVT-301 treatment group) or enters the TV/OV1 visit (if in the observational cohort), whether or not the patient completes the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a patient withdrawing prematurely should be selected from the following standard categories of early termination:

- *Adverse Event*: Clinical or laboratory events occurred that in the medical judgment of the investigator for the best interest of the patient are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication.
- *Death*: The patient died.
- *Withdrawal of Consent*: The patient desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the patient gave a reason for withdrawing, it should be recorded in the eCRF.

- *Protocol Violation*: Significant findings indicating that the study investigator or patient failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The violation necessitated premature termination of the patient from the study.
- *Lost to Follow-Up*: The patient stopped coming for visits, and study personnel were unable to contact the patient.
- *Other*: The patient was terminated for a reason other than those listed above (to be specified on the eCRF).

9. TREATMENTS

9.1. Details of Study Treatment for the CVT-301 Treatment Group

Basic information about the study drug for the CVT-301 treatment group is provided in Table 1 and details regarding the reduced-dose study drug for patients with tolerability issues are provided in Table 2.

Table 1 Details of Study Drug

	CVT-301 (Test Product)
Name	CVT-301 (levodopa inhalation powder)
Manufacturer	Civitas Therapeutics, Inc.
Doses	2 CVT-301 capsules delivering a target nominal respirable dose of approximately 50 mg LD FPD
Route	Inhaled via the CVT-301 inhaler
Formulation	Capsules of levodopa inhalation powder
Capsule Strength	Capsule fill weight of LD: 42 mg Respirable LD dose/FPD per capsule: 25.0 mg (Emitted LD per capsule: 35 mg)

Abbreviations: FPD=fine particle dose; LD=levodopa.

Table 2 Details of Reduced-Dose Study Drug[1]

	CVT-301 (Test Product)
Name	CVT-301 (levodopa inhalation powder)
Manufacturer	Civitas Therapeutics, Inc.
Doses	2 CVT-301 capsules delivering a target nominal respirable dose of approximately 35 mg LD FPD
Route	Inhaled via the CVT-301 inhaler
Formulation	Capsules of levodopa inhalation powder
Capsule Strength	Capsule fill weight of LD: 30 mg Respirable LD dose/FPD per capsule: 17.5 mg (Emitted LD per capsule: 25 mg)

Abbreviations: FPD=fine particle dose; LD=levodopa.
[1] Reduced-dose study drug kits will be permitted for patients with tolerability issues. Refer to Section 10.3 for details on when this dose may be utilized.

9.1.1. CVT-301 Capsule for Inhalation (Test Product)

CVT-301 capsules are packaged into blister strips composed of foil-foil blister strips.

9.1.2. Sham Capsule for Inhalation

Sham inhalation capsules are empty size 00 HPMC capsules that will be used with the inhaler to train both staff and patients on the use of the CVT-301 inhaler. Sham capsules are packaged into foil-foil blister strips. A training inhaler and sham capsules will be provided to patients for the inhaler training sessions.

9.1.3. Civitas CVT-301 Inhaler

CVT-301 capsules will be delivered using the CVT-301 inhaler, which is a 5-inch-long, single-capsule-based, breath-actuated inhaler.

9.1.4. Packaging of Inhaled Study Treatment

Study drug supplies will be packaged into study drug kits. Each study drug kit will contain 20 blister strips of CVT-301 capsules (an 8-day supply), an inhaler, and the IFU. At TV1, TV2, TV3, TV4, and TV5, each patient in the CVT-301 treatment group will be issued a sufficient supply of study drug kits to accommodate the visit windows. Kits will be stored at room temperature environment (25°C [77°F]) at the clinical sites and may not be stored in excessive

heat (i.e., above 40˚C [104˚F]) or excessive cold (i.e., below 2˚C [36˚F]). Patients will be told to store the kits containing the inhalers and study drug at room temperature and will be required to return unused study drug, used capsules, and the inhaler from each kit at their subsequent clinic visit.

Reduced-dose study drug kits (at a target nominal dose of 35 mg LD FPD) will be packaged, stored, and accounted for in a similar manner. These kits are to be utilized for patients unable to tolerate CVT-301 at a target nominal dose of 50 mg LD FPD, as described in Section 10.3.

All Investigational Product Complaints must immediately be reported to the sponsor.

Site study personnel should immediately notify the Site Monitor and provide a description of the complaint. Sponsor representatives from IP Supply or Quality Assurance Departments will work with the Site Monitor or site study personnel to gather further information needed. Note that this is for IP quality complaint notification, not for AE reporting.

9.2. Randomization and Administration of Study Treatment

9.2.1. Randomization and Assignment of Study Treatment

Following completion of SV2 and prior to randomization, the patients' eligibility criteria will be reviewed by delegated staff. Upon confirmation of eligibility, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). Sites must allow 7 business days between time of randomization and the first treatment visit (TV1) to allow time for drug to be shipped and received.

Eligible patients will be randomized in a 2:1 ratio to CVT-301 treatment (CVT-301 50 mg PD FPD) or the observational cohort. Randomization will be differentiated by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each treatment group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%). Patients who previously completed the CVT-301-002 and CVT-301-003 studies will be assigned only to the CVT-301 treatment group. The study is an open-label study, so patients and clinical staff will not be blinded to study group assignment.

9.2.2. Defining "Time 0" (T0) (for the CVT-301 Treatment Group)

During inhaler training, patients will be instructed to hold their breath following each inhalation for approximately 5 seconds after administration of each capsule, in accordance with the IFU. For the purposes of timing study assessments, "Time 0" (T0) is defined as the *time of completion of inhalation of the last capsule of inhaled study treatment* administered (i.e., beginning of the final breath hold). In the event that a capsule needs to be re-inhaled, T0 is at the end of the re-inhalation administration.

9.3. Treatment Accountability and Compliance (for the CVT-301 Treatment Group)

The pharmacist or study coordinator will maintain records of study kits delivered to the study site, the inventory at the site, the distribution to and use by each patient, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities,

batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and trial patients. Investigators will maintain records that document adequately that the patients were provided with the correct study treatment kits and will reconcile the products received from the drug dispensing center. Investigational product will not be returned until accountability has been fully monitored.

In-clinic administration of study drug will be supervised by study personnel, and at-home PD Diary data will be reviewed to ensure patient compliance.

9.4. Prior and Concomitant Illnesses and Medications

9.4.1. Prior and Concomitant Illnesses

Investigators should document all prior significant illnesses that the patient has experienced within 5 years prior to screening. New illnesses present at the time when informed consent is given and for the duration of the study are to be documented as AEs on the eCRF.

Clinic staff will contact patients 4 to 6 days prior to TV/OV1 to remind them that they must be symptom-free of any flu-like syndrome or other respiratory infection for at least 3 days prior to the visit and that they should contact the site if an intervening illness occurs prior to TV/OV1. If the patient has any of these symptoms within this time period, this visit will be rescheduled once these symptoms have been resolved for at least 3 days. The screening period may be extended for up to 2 weeks to accommodate this recovery.

9.4.2. Prior and Concomitant Medications

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use. In addition, medications taken by or administered to the patient for 3 months prior to SV1 will be recorded in the eCRF.

Patients must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with an LD/DDI-containing regimen, when not including Rytary, and stable for at least 6 weeks prior to SV1 when including Rytary. The oral LD regimen must include doses at least 3 times during the waking day and a total daily LD dose of ≤1600 mg (exclusive of PRN LD-containing medications). During the study, all patients' standard PD medication regimen may be altered as needed to manage PD symptoms. Additions to and/or modification of the patient's usual PD treatment regimen may include any PD treatments that are currently approved in the patient's region. Oral PRN LD formulations are not permitted for CVT-301-treated subjects from TV/OV1 to TV/OV6. For CVT-301-treated patients, the total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day. In the event that the dose or schedule of the patient's oral LD-containing medication does change during the treatment period, record all changes in medication, including the total LD dose, in the eCRF.

If the patient is treated with dopamine agonists, COMT inhibitors, monoamine oxidase-B (MAO-B) inhibitors, he/she must be on a stable dose for at least 4 weeks prior to SV1 and must remain stable throughout the study. If the patient is on anti-depressant medication or other non-LD-containing PD medications, the dose must be stable for at least 4 weeks prior to SV1.

In countries and/or municipalities where the use of marijuana-based products is legal for medical purposes, patients who may be using medical marijuana as a treatment for their PD may be enrolled into the study as long as they meet the following parameters:

1. Medical marijuana has been prescribed to the patient prior to the date of informed consent. Patients who have not already been prescribed medical marijuana prior to beginning study participation may not begin medical marijuana use during their participation in the study.
2. Medical marijuana is not being used to treat any contraindicated condition as defined in the protocol (i.e., glaucoma, cancer, etc.).
3. Patients meet all other eligibility criteria (including spirometry).
4. Patients must agree not to use medical marijuana (smoking, ingestion or any other potential route of administration) on clinic days, before coming to the clinic or while in the clinic, until all procedures have been completed and they are discharged.

All patients in this study will take their usual prescribed PD medications during the study including on the morning of each in-clinic treatment/observational visit. The timing of the administration of the usual morning dose of PD medications may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. On designated in-clinic dosing days for CVT-301-treated patients, if the patient converts to an ON state after the study drug has been administered, and all post-treatment study procedures have been performed, the patients will resume their standard schedule of PD medications.

In addition, for CVT-301-treated patients, the inhaled study drug will be used for the treatment of OFF episodes in accordance with this protocol. Patients should not take inhaled study drug within 45 minutes following their prior dose of standard oral PD medication. Also, patients should not use inhaled study drug for the treatment of early morning OFF. Otherwise, study drug may be used during the waking day for the treatment of OFF episodes that occur in between doses of the patients' standard oral PD medications. Patients in the CVT-301 treatment group should *not* take oral PRN PD medications to manage their OFF states throughout the treatment period.

During in-clinic evaluation days, if inhaled study drug does not provide sufficient relief of the OFF state to enable the patient to return to an ON state by 60 minutes post-dose, patients will receive their usual oral dose of PD medication(s) and may be discharged home when all study assessments are completed. At home, in the event that an OFF state is not sufficiently resolved within 45 minutes of completing the last inhalation of CVT-301, patients will be permitted to take their next scheduled dose of their usual prescribed PD medication; patients may not re-dose with inhaled study drug for that OFF episode. Patients may use inhaled study drug to manage only up to 5 OFF episodes per day. If patients experience more than 5 OFF episodes per day, they should adhere to their usual standard oral regimen to manage these additional episodes.

Prohibited Therapies

Medication to treat study-emergent and treatment-emergent illness(es) is generally permitted; however, the following therapies/products are expressly prohibited throughout the study:

- Apomorphine. Use of apomorphine is restricted to a frequency of once per day. Concomitant use of study medication (CVT-301) with apomorphine, i.e. use within the same OFF episode, is excluded.
- Reserpine. Patients must not have used reserpine for at least 3 months prior to SV1 and must not use it for the duration of the study.
- Antipsychotic medications. Patients must not have used antipsychotic medications for at least 12 months prior to SV1 and must not use them for the duration of the study. Exceptions: certain low-dose atypical antipsychotic agents are allowed if the dose has been stable for at least 4 weeks prior to screening (for example, quetiapine ≤50 mg/day, risperidone ≤1 mg/day, and olanzapine ≤2.5 mg/day) if used for non-psychosis-related conditions.
- Other non-neuroleptic dopamine antagonists or *non-specific* monoamine oxidase inhibitors (MAOIs). Patients must not have used any of these agents for at least 3 months prior to SV1 and must not use them for the duration of the study. Exception: In regions where it is approved, domperidone is permitted during the study if the maximum daily dose does not exceed 60 mg and if the dose has been stable for at least 4 weeks prior to screening.
- Investigational drugs. Patients must not have taken any investigational drugs (including investigational formulations of marketed products) for at least 4 weeks or 5 half-lives (whichever is longer) prior to SV1 and must not use them for the duration of the study.
- Smoking. Current smokers are permitted to participate in the study provided that they meet other eligibility requirements (spirometry and concomitant respiratory illness). They must agree to and are able to abstain from smoking on the day of each in-clinic visit while in-clinic through completion of all assessments for that visit day (including screening visits and in-clinic treatment/observational visits).
- Oral PRN PD medications for CVT-301-treated patients during the treatment period. All patients are permitted to take oral PRN PD medications during the screening period. However, *oral PRN PD medications are not permitted during the treatment period for CVT-301-treated patients.*

10. STUDY PROCEDURES

The overall schedule of assessments is provided in Appendix 1, and specific time and events schedules for the screening visits and in-clinic treatment/observational visits are provided in Appendix 2 through Appendix 15. Unless otherwise specified, all assessments will be performed by the investigator or other assigned personnel.

10.1. Screening Period

Patients will undergo a screening period of up to 35 days before entering the treatment period. The screening period will consist of 2 scheduled clinic visits: SV1 and SV2. The screening period may be extended an additional 7 days if repeat screening assessments are required. At

SV1, after patients have provided informed consent, they will be assessed for study eligibility in ON and OFF states. At SV2, any screening assessment performed at SV1 will be repeated if needed to verify or re-check results, and inhaler training will be performed.

Patients who do not develop an adequate OFF or ON period at SV1 will be invited to re-attend on a subsequent day, but will be withdrawn if further observation shows they are unable to turn OFF during a regularly scheduled study visit in accordance with the procedures. In addition, if a patient is unable to complete all assessments or training at the scheduled SV1, he/she may be rescheduled to repeat the visit, and/or to return to the clinic for additional training.

10.1.1. Screening Visit 1 (within 35 days prior to TV/OV1)

Patients should be instructed to bring all of their medications with them to SV1. The following list is a suggested schedule for this visit, with assessments outlined in Appendix 2. (Note: If a patient arrives at the clinic in an OFF state, assessments will be done in an OFF state first, then they will be repeated in an ON state after the patient has taken his/her standard dose of LD-containing medications and converted to an ON state.)

1. Give the patient an explanation of the purpose and nature of the study, and receive his/her voluntary written informed consent before any study procedures are performed.
2. Determine eligibility according to inclusion/exclusion criteria.
3. Record medical history (including smoking history), concurrent medical conditions, and PD history.
4. Confirm diagnosis of PD using Steps 1 and 2 of the UK Brain Bank criteria in the ON state. (Refer to Section 11.3.1 and Appendix 18.)
5. Use the modified Hoehn and Yahr scale to assess PD severity (in an ON state). (Refer to Appendix 19.)
6. Record the estimated average number of hours of OFF time during the waking day (not including early morning OFF time) as reported by the patient. Eligible patients must have, by self-report, motor fluctuations with daily OFF time averaging at least 2 hours per day (not including early morning OFF time and which will require confirmation using the PD Diary over a period of 3 consecutive days).
7. Check and record all PD medications (including the number of times per day that LD-containing medications are administered and total daily LD dose) and other concomitant medications. Confirm that the patient is on stable dosages of PD medications (at least 2 weeks for the LD-containing medication, and 4 weeks for the other PD medications). Ensure that specified concomitant medications have been stabilized in accordance with protocol-defined criteria.
8. Perform the MMSE (in an ON state).
9. Perform a full physical examination.
10. Complete the Pulmonary Function Baseline Questionnaire.
11. Record a 12-lead ECG (after patient has been in a supine position for at least 5 minutes, as per Section 11.1.3).

12. Measure standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR). Standard vital signs should be taken after the patient has rested in a supine or semi-supine position for at least 5 minutes, and orthostatic vital signs should be taken after the patient has been standing for 2 minutes (see Section 11.1.2 for suggested detailed procedures).
13. Perform spirometry to measure FEV1, FVC, and FEV1/FVC ratio to assess lung function (this must be performed with the patient in the ON state).
14. Perform UPDRS Part 3 in an ON state.
15. Train patients on how to assess their ON and OFF states and how to record their waking ON/OFF status in a screening PD Diary (time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia, and time asleep).
16. Perform concordance testing with the patients (while in the ON and OFF states) for recognizing different ON/OFF states and recording them appropriately in the PD Diary. Patients will be tested for competence at self-rating and must be within 75% concordance with the ratings of the examiner (at least 3 out of 4 half-hour sessions over the course of 2 hours); if concordance is not reached, the observation period may be extended for an additional 2 hours to obtain agreement on at least 6 of 8 half-hour sessions. The same training and testing may be repeated at an unscheduled visit between SV1 and SV2 or at SV2. If patients return for an unscheduled visit between SV1 and SV2 for concordance training and testing, the visit must occur more than 3 days prior to SV2. If patients do not achieve 75% concordance by the end of SV2, they will be considered screen failures.
17. Introduce the inhaler and perform inhaler training using sham capsules with the CVT-301 inhaler while in the ON state.
18. Take samples for clinical laboratory tests, including a serum pregnancy test for females of childbearing potential (see Appendix 17 for a list of laboratory parameters assessed). Patients do not need to be in a fasted state at the time of the laboratory sample; however, fasted status will be documented (with fasting defined as at least 4 hours following the last meal or snack).
19. Patients will remain in the clinic and further PD medications will be withheld until they turn into an OFF state.
20. Perform the assessments in the following suggested order while the patient is in an OFF state: spirometry, UPDRS Part 3, patient training on self-report of ON/OFF states, and inhaler training using sham capsules with the CVT-301 inhaler.
21. Distribute the PD Diary; train patients to record time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia, and time asleep for the 3 consecutive days prior to SV2.
22. Distribute the Screening ON/OFF Episodes Log; train patients to record the number of OFF episodes experienced by the patients during their waking day for the 3 consecutive days prior to SV2.

23. If needed, train caregivers on how to prepare inhalers for patients and how to complete the PD Diary and Screening ON/OFF Episodes Log (diaries will be completed based on the *patient report*).
24. Monitor for AEs throughout the visit.
25. Review with patients (and their caregivers) the planned schedule of events for the remaining study visits, and the responsibilities of self-administration of study drug and of recording information in the at-home diaries. Schedule the next visit.
26. Ask patients to bring the PD Diary, the Screening ON/OFF Episodes Log, and all of their PD medications with them at SV2, to take their usual morning medications prior to the visit, and to note the time when they took them.

The next visit will be scheduled. The site will call the patient approximately 4 days before SV2 to confirm the next study visit and to remind patients of the study procedures and the requirements noted in Item 26 in the above list.

10.1.2. Screening Visit 2 (at least 4 days after SV1)

The purpose of this visit is as follows: (a) to repeat any screening assessment performed at SV1 if needed to verify or re-check results for eligibility and safety, (b) to review the PD Diary and Screening ON/OFF Episodes Log to confirm eligibility (if these were not done correctly, the site may have to reschedule this visit) (c) to perform spirometry and vital signs, if needed to verify or re-check results, and (d) to re-train the patient on proper inhalation technique with the inhaler and on recording PD Diary and Screening ON/OFF Episodes Log information. For the 3 consecutive days prior to SV2, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for SV2, the patient will take all of their usual prescribed non-PD medications and PD medications, including LD-containing PD medications.

The following list is a suggested schedule for this visit:

1. Upon the patient's arrival to the clinic, reconfirm eligibility from SV1, including review of the PD Diary and the Screening ON/OFF Episodes Log. In the PD Diary, if <80% of the awake time is filled in for the 3-day period, the diary training and concordance testing must be repeated. The training and concordance testing will also be repeated if the patient has not reached 75% or greater concordance with the examiner at SV1 or at an unscheduled visit between SV1 and SV2.
2. Record any changes in the usual PD medication dose and regimen.
3. Review concomitant medications.
4. Perform inhaler re-training using sham capsules with the CVT-301 inhaler and IFU. If the patient has undergone inhaler training in both the ON and OFF states at SV1, it may be done in either state at this visit.
5. Patient training on assessment of the ON/OFF state will be repeated while the patient is in the ON and OFF states as needed.
6. Distribute a new PD Diary and Screening ON/OFF Episodes Log, and instruct the patients to complete both of them for the 3 consecutive days prior to TV/OV1.

7. Schedule a DLco assessment to be performed at an outside pulmonary laboratory after SV2 and prior to treatment assignment/randomization. The assessment should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry.
8. If needed, the following assessments from SV1 may be completed or repeated: MMSE (in ON state); full physical examination; 12-lead ECG; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); spirometry (in ON and OFF states); UPDRS Part 3 (in ON and OFF states); ON/OFF concordance testing (in ON and OFF states); and clinical laboratory test, including serum pregnancy test, if applicable (with documentation of fasting status).
9. Monitor for AEs throughout the visit.

If a patient is unable to complete a screening assessment at SV2, an additional visit (repeat SV2) may be scheduled prior to eligibility determination and randomization. Any repeat assessments should be performed in the respective motor state as described for SV1. The site will contact patients by telephone 4 to 6 days prior to TV/OV1 to confirm the DLco assessment has been done, to confirm the next study visit, and to remind patients of the study procedures required prior to the next scheduled study visit (including completion of the PD Diary and Screening ON/OFF Episodes Log). In addition, the site should remind the patients during the call that they must be symptom-free of any flu-like syndrome or other respiratory infection for at least 3 days prior to prior to TV/OV1 and that they should contact the site if an intervening illness occurs prior to TV/OV1. If the patient has any of these symptoms within this time period, this visit will be rescheduled once these symptoms have been resolved for at least 3 days. The screening period may be extended for up to 2 weeks to accommodate this recovery.

10.2. Randomization to Study Drug

Following completion of SV2 and prior to randomization, the patients' eligibility criteria will be reviewed by delegated staff. Eligible patients will be randomized in a 2:1 ratio to CVT-301 treatment group (CVT-301 50 mg PD FPD) or the observational cohort. Randomization will be differentiated by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each treatment group and by screening spirometry (FEV1 <60% of predicted *or* FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted *and* FEV1/FVC ratio ≥70%). Sites must allow 7 business days between time of randomization and the first treatment visit (TV1) to allow time for drug to be shipped and received.

10.3. Treatment/Observational Period

Patients in both the CVT-301 treatment group and observational cohort are required to attend all of the in-clinic treatment/observational visits. For the CVT-301 treatment group, these visits will be treatment visits and for the observational cohort, these will be observational visits. The assessments and procedures for the in-clinic treatment/observational visits will differ for patients in the CVT-301 treatment group compared to the observational cohort.

All patients, regardless of treatment assignment, should continue with their usual prescribed standard PD medication regimen for the duration of the study which may be modified for symptomatic treatment during the study in accordance with usual practice.

Patients assigned to the CVT-301 treatment group may use the prescribed dose of CVT-301 as needed for the treatment of up to 5 OFF episodes per day in addition to their standard PD medications which may be modified as needed for symptomatic treatment over the 12-month study. Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode) to deliver the dose.

Patients assigned to the observational cohort will not receive CVT-301 but will be managed with their prescribed PD medications, which may be modified as needed for symptomatic treatment over the 12-month study.

For both the CVT-301 treatment group and the observational cohort, additions to and/or modification of the patient's usual PD treatment regimen may include any PD treatments that are currently approved in the patient's region. However, oral PRN LD formulations are not permitted for CVT-301-treated subjects (refer to Section 9.4.2 for a list of prohibited treatments and prohibited medications). For CVT-301-treated patients, the total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day. Changes in the medications, doses, or frequency of medication administration will be documented in the eCRF.

During this period, CVT-301 patients will self-administer inhaled study treatment (CVT-301 50 mg LD FPD) up to 5 times daily to treat OFF episodes during their waking day. The first dose of open-label study drug will be given in the clinic at TV1; patients will be given study drug kits at TV1, TV2, TV3, TV4, and TV5.

The treatment/observational period includes 6 separate in-clinic treatment/observational visits over approximately 1 year. The sequence of timing the patient's morning dose of PD medications and clinic arrival should be discussed with the patient to increase the likelihood that the patient will reliably be in an ON state upon arrival and turn OFF during the office visit. Patients will take their morning dose of PD medications and should eat their standard breakfast prior to arrival at the clinic.

If a patient in the CVT-301 treatment group develops significant tolerability concerns that in the opinion of the investigator are of a severity that should necessitate a reduction in dose, including, but not limited to the exacerbation or worsening of troublesome dyskinesia, other problematic dopaminergic symptoms, or other tolerability concerns, a dose reduction from 2 capsules (50 mg LD FPD) to 1 capsule (25 mg LD FPD) per treated episode may be permitted. The medical monitor should be contacted, and the investigator should use his/her clinical judgment to determine whether an additional visit is required and what assessments should be performed (e.g., physical examination, spirometry, etc.). The patient should continue to use 1 capsule (25 mg LD FPD) per treated episode for a period of at least 1 week. If the investigator determines that the tolerability issue has adequately resolved and that the patient has tolerated this dose for at least 1 week, the patient may at that point either resume taking the original dose (2 capsules [50 mg LD FPD] per treated episode) or come into the clinic for an unscheduled visit to receive a reduced-dose study drug kit (35 mg LD FPD). Clinical staff will call the patient 1 to 2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has

escalated back to the full dose (50 mg LD FPD per treated episode) has another tolerability concern that in the opinion of the investigator is of a severity that should necessitate a second reduction in dose, an unscheduled visit will be required and a reduced-dose study drug kit (35 mg LD FPD per treated episode) will be provided. He/she will remain on the reduced dose (35 mg LD FPD) for the remainder of the study; he/she will not be eligible for any additional up-titration in dose.

Refer to Appendix 2 through Appendix 15 for tables of study assessments at each visit during the treatment period.

10.3.1. Telephone Calls Before Treatment/Observational Visits

- Telephone calls should be made to patients 4 to 6 days before TV/OV1 for the following reasons: to confirm the DLco assessment has been done (must be completed prior to TV/OV1); to confirm the next study visit; to remind patients to complete the PD Diary and the Screening ON/OFF Episodes Log for the 3 consecutive days prior to the visit; to remind them to bring the PD Diary, Screening ON/OFF Episodes Log, and all of their PD medications with them to the visit; to remind them to take their usual morning medications and eat their standard breakfast prior to the visit; and to remind them to note the time when they take these morning medications. In addition, the site should remind patients that they must be symptom-free of any flu-like syndrome or other respiratory infection for at least 3 days prior to the visit and that they should contact the site if an intervening illness occurs prior to TV/OV1. If a patient has any of these symptoms within this time period, reschedule this visit after these symptoms have been resolved for at least 3 days. The screening period may be extended for up to 2 weeks to accommodate this recovery.
- Telephone calls should be made to patients in the CVT-301 treatment arm 1 to 3 days after TV1 to address any potential concerns or challenges with the inhaler systems or Inhaled Dosing Log.
- Telephone calls should be made to patients in the CVT-301 treatment group 2 weeks (± 3 days) before TV2, TV3, TV4, and TV5, and TV6 for the following reasons: to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log; to monitor for any AEs; to confirm the DLco assessment has been done/scheduled (prior to TV3, TV4, TV5, and TV6); to confirm the next study visit; to remind patients to complete the PD Diaries for the 3 consecutive days prior to TV2, TV3, TV4, TV5, and TV6; to remind patients to complete the Inhaled Dosing Log every day during the treatment period; to remind them to bring their PD Diaries, Inhaled Dosing Logs, study drug kits, and all of their PD medications with them to the visits; to remind them to take their usual morning medications and eat their standard breakfast prior to the visits; to ask how many empty study drug kits will be returned at the next visit; and to remind them to note the time when they take their usual morning medications.
- Telephone calls should be made to the patients in the observational cohort 2 weeks (± 3 days) prior to OV2 to monitor for AEs and to confirm the next study visit, and prior

to OV3, OV4, OV5, and OV6 to monitor for AEs, to confirm that the DLco assessment has been done/scheduled, and to confirm the next study visit.

10.3.2. Treatment Visit/Observational Visit 1 (at least 7 days after SV2)

10.3.2.1. Treatment Visit 1 for the CVT-301 Treatment Group

Patients will complete the Screening ON/OFF Episodes Log and PD Diary for the 3 consecutive days prior to TV1.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of arrival for TV1 should be scheduled to increase the likelihood that patients will be in the ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all of their usual prescribed PD medications.

On Arrival to the Clinic

The following list is a suggested schedule for this visit:

- Collect, review, sign, and date the PD Diary and Screening ON/OFF Episodes Log and document whether these were completed correctly.
- Confirm that the DLco assessment has been performed. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in the usual PD medication dose/regimen.
- Record all concomitant medications.
- Perform the PDQ-39 in an ON state.
- Perform a brief physical examination.
- Patients will complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Patients will complete the UPDRS Part 4 (Questions 32-35 and 36-39).
- Perform a 12-lead ECG.
- Record standard and orthostatic BP and HR. Record RR.
- Perform spirometry (preferably performed in the ON state; record the patient's motor state on the spirometry source record).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Perform the baseline assessments using the C-SSRS, Epworth Sleepiness Scale, and the QUIP.
- Distribute the PD Diary and review instructions for completion for recording time asleep, time OFF, time ON without dyskinesia, time ON with non-troublesome

dyskinesia, and time ON with troublesome dyskinesia (to be completed for the 3 consecutive days prior to TV2, TV3, TV4, TV5, and TV/6).

- Distribute the Inhaled Dosing Log and review instructions for completion for recording the number of times the inhaler was used and the number of capsules used for each inhalation treatment (to be completed daily throughout the 12-month treatment period).
- Distribute study drug kits to patients. Instruct patients to collect used empty capsules and return them at the next visit along with the PD Diary, Inhaled Dosing Log, and other study supplies.
- Re-train patients on the proper use of the inhaler with sham capsules, including a review of the IFU.

Study Drug Dosing

Immediately pre-dose, perform a spirometry assessment (record the patient's ON/OFF state on the spirometry source record). Under clinic staff supervision, preferably between 2 and 5 hours after receiving their standard dose of PD medication (in the OFF state), patients will prepare and self-administer their first dose of study drug from the study drug kits provided (i.e., 2 capsule inhalations of CVT-301). Patients will be permitted sips of water between capsule inhalations as needed. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

Note: Instructions for how to properly use the CVT-301 system are outlined in the Instructions for Use document that is included with every CVT-301 study kit. Refer to Appendix 21 for additional system information.

Post-dose (10 – 60 minutes)

The following post-dose safety evaluations will be performed:

- Record vital signs (standard and orthostatic BP and HR) at 20 and 60 minutes. post-dose.
- Record RR at 10, 20, 30, and 60 minutes post-dose.
- Monitor for AEs throughout the visit.

Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes). The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 1 to 3 days after TV/OV1 to monitor for AEs and to address any potential concerns or challenges with the inhaler systems or Inhaled Dosing Log. Additionally, clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) before each visit for TV2, TV3, TV4, TV5, and TV6 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled (prior to TV3, TV4, TV5, and TV6), to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and also to remind patients of the study procedures

required prior to the next scheduled study visit (including completion of the PD Diary and Inhaled Dosing Log).

10.3.2.2. Observational Visit 1 for the Observational Cohort

Patients will complete the Screening ON/OFF Episodes Log and PD Diary for the 3 consecutive days prior to OV1.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of arrival for OV1 should be scheduled to increase the likelihood that patients will be in the ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all of their usual PD medications.

On Arrival to the Clinic

The following list is a suggested schedule for this visit:

- Collect, review, sign, and date the PD Diary and Screening ON/OFF Episodes Log and document whether these were completed correctly.
- Confirm that the DLco assessment has been performed. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record all concomitant medications.
- Perform the PDQ-39 in an ON state
- Perform a brief physical examination.
- Patients will complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Record standard and orthostatic BP and HR. Record RR.
- Perform a 12-lead ECG.
- Perform spirometry (preferably performed in the ON state; record the patient's motor state on the spirometry source record).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Perform the baseline assessments using the C-SSRS, Epworth Sleepiness Scale, and the QUIP.
- Monitor for AEs.

The next visit will be scheduled and the patient will be discharged from the visit.

10.3.3. At-Home Dosing for the CVT-301 Treatment Group

At TV1, TV2, TV3, TV4, and TV5, patients in the CVT-301 treatment group will receive study drug kits and the IFU to take home with them. Patients will be instructed to take their standard

oral PD medications as prescribed on their usual schedule of administration, which may be modified as needed for symptomatic treatment during the 12-month study. Additions to and/or modification of the patient's usual PD treatment regimen may include any PD treatments that are currently approved in the patient's region. Oral PRN LD formulations are not permitted for these patients (refer to Section 9.4.2 for a list of prohibited treatments and prohibited medications). The total daily LD dose of the modified PD treatment regimen (not including CVT-301) must not exceed 1600 mg per day.

Patients will be instructed to administer inhaled study drug up to 5 times during the waking day *as close as possible to the time when they begin to experience OFF symptoms*. The PD symptomatology defining the onset of an OFF state may vary by patient, but typically is indicated by the return of PD motor symptoms such as tremor or bradykinesia; for some patients, OFF episodes may be heralded by non-motor symptoms (e.g., pain or anxiety) shortly prior to the appearance of motor symptoms.

Study drug may **not** be used for the treatment of early morning OFF periods (i.e., morning akinesia). Patients may not take their inhaled study drug within 45 minutes following their previous dose of standard oral PD medication. These patients may not take oral PRN medications to manage OFF states during the study.

In the event that an OFF state is not sufficiently resolved within 45 minutes of completing the last capsule inhalation, patients may resume their usual prescribed PD medication, if they have not already done so (i.e., according to their standard dose schedule/regimen); patients may not re-dose with inhaled study drug for that episode. If patients experience more than 5 OFF episodes per day that require treatment, they should adhere to their standard oral regimen for management of any additional OFF episodes; they may not treat these episodes with additional inhalations of study drug.

Patients will complete the PD Diary for the 3 consecutive days prior to TV2, TV3, TV4, TV5, and TV6. Patients will complete the Inhaled Dosing Log every day during the 12-month treatment period. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV1 and 2 weeks (± 3 days) prior to each visit for TV2, TV3, TV4, TV5, and TV6.

They will bring the PD Diary, Inhaled Dosing Log, empty capsules, inhalers, and unused supplies to the each clinic visit. If the patient begins to run low on study supplies in between treatment visits, they should contact the site. Unused supplies can be re-dispensed to the patient at each clinic visit, in addition to a sufficient number of new study drug kits to supply the patient until his/her next visit. Note: Any open kit (even if partially unused) may not be re-dispensed.

10.3.4. Treatment Visit/Observational Visit 2 (1 month [4 weeks ±5 days] after TV/OV1)

10.3.4.1. Treatment Visit 2 for the CVT-301 Treatment Group

Patients will complete the PD Diary for the 3 consecutive days prior to TV2 and the Inhaled Dosing Log daily throughout the treatment period. Patients will bring their usual PD medications, the PD Diary, Inhaled Dosing Log, used supplies, including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home).

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Collect used empty capsules and inhalers and unused supplies.
- Record any changes in the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in concomitant medications.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Perform the C-SSRS.
- Distribute new study drug kits.
- Review inhaler training with the patient.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
- Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled CVT-301. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia and note in the eCRF if the patient experiences dyskinesia at any time within the 60-minute post-dose period.

Also, if applicable, record the maximum severity of dyskinesia during the 60-minute post-dose period.

- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Monitor patients for AEs throughout the visit.

Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes).

The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) before TV3 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule a DLco assessment within 2 weeks prior to TV3. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary technician) in the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be first, followed by DLco, and then spirometry.

10.3.4.2. Observational Visit 2 for the Observational Cohort

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Perform the C-SSRS.
- Monitor patients for AEs.

The next study visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to OV3 to monitor for AEs, to confirm that the DLco assessment has been done/scheduled, and to confirm the next study visit. The DLco assessment will be scheduled to occur within 2 weeks prior to the next visit and should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

10.3.5. Treatment Visit/Observational Visit 3 (3 months [12±2 weeks] after TV/OV1)

10.3.5.1. Treatment Visit 3 for the CVT-301 Treatment Group

Patients will complete the PD Diary for the 3 consecutive days prior to TV3 and the Inhaled Dosing Log daily throughout the treatment period. Patients will bring their usual PD medications, the PD Diary, Inhaled Dosing Log, used supplies, including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Collect used empty capsules and inhalers and unused supplies.
- Confirm that the DLco assessment was performed within 2 weeks prior to TV3. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in concomitant medications.
- Patients should complete the PGI-C preferably in the ON state, and this must be done prior to other study assessments.
- The C-SSRS should be completed.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.

- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Distribute new study drug kits.
- Review inhaler training with the patient.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
- Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment.Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled CVT-301. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia and note in the eCRF if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of dyskinesia during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Monitor patients for AEs throughout the visit.

Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes).

The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) before TV4 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule a DLco assessment within 2 weeks prior to TV4. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary

technician) in the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be first, followed by DLco, and then spirometry.

10.3.5.2. Observational Visit 3 for the Observational Cohort

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Confirm that the DLco assessment was performed within 2 weeks prior to OV3. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Perform the C-SSRS.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Monitor patients for AEs.

The next visit will be scheduled, and clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) prior to OV4 to monitor for AEs, to confirm the DLco assessment has been done/scheduled, and to confirm the next study visit. The DLco assessment will be scheduled to occur within 2 weeks prior to the next visit and should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

10.3.6. Treatment Visit/Observational Visit 4 (6 months [24±2 weeks] after TV/OV1)

10.3.6.1. Treatment Visit 4 for the CVT-301 Treatment Group

Patients will complete the PD Diary for the 3 consecutive days prior to TV4 and the Inhaled Dosing Log daily throughout the treatment period. Patients will bring their usual PD medications, the PD Diary, Inhaled Dosing Log, used supplies, including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home).

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Collect used empty capsules and inhalers and unused supplies.
- Confirm that the DLco assessment was performed within 2 weeks prior to TV4. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in concomitant medications.
- PDQ-39, PGI-C, UPDRS Part 2, and S&E ADL should be completed, preferably in an ON state, and must be done prior to other study evaluations.
- Patients will complete the UPDRS Part 4 (Questions 32-35 and 36-39).
- The C-SSRS, Epworth Sleepiness Scale, and QUIP should be completed.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Distribute new study drug kits.

- Review inhaler training with the patient.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
- Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled CVT-301. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia and note in the eCRF if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of dyskinesia during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Monitor patients for AEs throughout the visit.

Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes).

The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) before TV5 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled, to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule a DLco assessment within 2 weeks prior to TV5. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry.

10.3.6.2. Observational Visit 4 for the Observational Cohort

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further PD medications will be used until following completion of

all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Confirm that the DLco assessment was performed within 2 weeks prior to OV4. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Perform the PDQ-39, UPDRS Part 2, and S&E ADL (each preferably in the ON state and must be done prior to other study evaluations).
- Perform the C-SSRS, Epworth Sleepiness Scale, and the QUIP.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Monitor patients for AEs.

The next visit will be scheduled and the clinic staff will arrange to call the patient 2 weeks prior to OV5 to monitor for AEs, to confirm the DLco assessment has been done/scheduled, and to confirm the next study visit. The DLco assessment will be scheduled to occur within 2 weeks prior to the next visit and should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

10.3.7. Treatment Visit/Observational Visit 5 (9 months [36±2 weeks] after TV/OV1)

10.3.7.1. Treatment Visit 5 for the CVT-301 Treatment Group

Patients will complete the PD Diary for the 3 consecutive days prior to TV5 and the Inhaled Dosing Log daily throughout the treatment period. Patients will bring their usual PD medications, the PD Diary, Inhaled Dosing Log, used supplies, including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the

investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home).

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Collect used empty capsules and inhalers and unused supplies.
- Confirm that the DLco assessment was performed within 2 weeks prior to TV5. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in concomitant medications.
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Perform the C-SSRS.
- Distribute new study drug kits.
- Review inhaler training with the patient.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
- Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled CVT-301. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia and note in the eCRF if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of dyskinesia during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Monitor patients for AEs throughout the visit.

Upon completion of the 60-minute observations, resumption of normal medications is permitted for the remainder of the day (the patient may use the inhaled study drug 4 more times at home after he/she leaves the clinic on that day if needed for OFF episodes).

The next visit will be scheduled. Clinic staff will arrange to speak with patients by telephone 2 weeks (± 3 days) before TV6 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled to confirm the next study visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule a DLco assessment within 2 weeks prior to TV6. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary technician) in the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be first, followed by DLco, and then spirometry.

10.3.7.2. Observational Visit 5 for the Observational Cohort

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Confirm that the DLco assessment was performed within 2 weeks prior to OV5. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Perform a brief physical examination.

- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Perform the C-SSRS.
- Monitor patients for AEs.

The next visit will be scheduled and the clinic staff will arrange to call the patient 2 weeks prior to OV6 to monitor for AEs, to confirm that the DLco assessment has been done/scheduled, and to confirm the next study visit. The DLco assessment will be scheduled to occur within 2 weeks prior to the next visit and should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

10.3.8. Treatment Visit/Observational Visit 6 / Early Withdrawal Visit (12 months [52±2 weeks] after TV/OV1)

10.3.8.1. Treatment Visit 6 / Early Withdrawal Visit for the CVT-301 Treatment Group

Patients will complete the PD Diary for the 3 consecutive days prior to TV6 and the Inhaled Dosing Log daily up until TV6. Patients will bring their usual PD medications, the PD Diary, Inhaled Dosing Log, used supplies including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further non-study PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Collect used empty capsules and inhalers and unused supplies.
- Confirm that the DLco assessment was performed within 2 weeks prior to TV6. If the DLco has not been completed prior to the visit, the visit must be rescheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record any changes in concomitant medications.

- Perform the PDQ-39, PGI-C, UPDRS Part 2, and S&E ADL (each preferably in the ON state and must be done before other assessments).
- Patients will complete the UPDRS Part 4 (Questions 32-35 and 36-39).
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.
- The C-SSRS, Epworth Sleepiness Scale, and QUIP should be completed.
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled CVT-301. The dosing time is defined to be when the patient's OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication. A new inhaler will be provided for this dose, and patients will use study drug from the supplies brought to the visit.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia and note in the eCRF if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of dyskinesia during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Monitor patients for AEs throughout the visit.

Once all of the assessments are complete, schedule the patient to undergo a DLco assessment 4 to 5 weeks after completion of TV6. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary technician) in the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be first, followed by DLco, and then spirometry.

10.3.8.2. Observational Visit 6 / Early Withdrawal Visit for the Observational Cohort

Patients will report to the clinic after having taken their usual PD medications prior to the visit. The timing of administration of the usual morning dose of PD medication may be adjusted by the investigator to accommodate the patient's and/or clinic's schedule. Following their usual morning PD medication, no further PD medications will be used until following completion of all assessments. The timing of arrival should be scheduled to increase the likelihood that patients will be in an ON state upon arrival (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Confirm that the DLco assessment was performed within 2 weeks prior to OV6. If the DLco assessment has not been completed prior to the visit, the study visit must be re-scheduled.
- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Perform the PDQ-39, UPDRS Part 2, and S&E ADL (each preferably in the ON state and must be before other study evaluations).
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform 12-lead ECG.
- Perform spirometry assessment (preferably in the ON state; however, if the patient is not in an ON state, perform the evaluation and record the motor state with each assessment).
- The C-SSRS, Epworth Sleepiness Scale, and QUIP should be completed.
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Monitor patients for AEs.

Once all of the assessments are complete, schedule the patient for a DLco assessment 4 to 5 weeks after OV6. The DLco assessment should be performed while the patient is in an ON state (as reported by the patient to the pulmonary technician) at the pulmonary function facility. As part of the procedure, a slow vital capacity will be performed, followed by DLco, and then spirometry.

10.3.9. Early Withdrawal Visit

Patients in the CVT-301 treatment group who withdraw prematurely will complete the TV6 assessments for the CVT-301 patients (see Section 10.3.8.1), except for the pre-TV6 DLco assessment, at the time of withdrawal. Patients in the observational cohort who withdraw

prematurely will complete the OV6 assessments for the observational cohort (see Section 10.3.8.2), except for the pre- OV6 DLco assessment, at the time of withdrawal.

All patients who withdraw early, regardless of treatment group, will be scheduled to undergo a DLco assessment 4 to 5 weeks after completion of the Early Withdrawal Visit. The DLco assessment should be performed in an ON state (as reported by the patient to the pulmonary technician) in the pulmonary function facility. As part of the procedure, a slow vital capacity maneuver will be first, followed by DLco, and then spirometry.

10.3.10. Unscheduled Visits

An unscheduled visit may occur when indicated at the discretion of the Investigator. The following are potential circumstances for unplanned visits:

- If concordance is not reached during SV1, the same training and testing may be repeated at an unscheduled visit between SV1 and SV2 or at SV2. If patients return for an unscheduled visit between SV1 and SV2 for concordance training and testing, the visit must occur more than 3 days prior to SV2.
- If a patient is unable to complete a screening assessment at SV2 (repeat SV2), an additional visit may be scheduled prior to eligibility determination and randomization. Any repeat assessments should be performed in the respective motor state as described for SV1.
- If a patient develops significant tolerability concerns that in the opinion of the investigator are of a severity that should necessitate a reduction in dose, including, but not limited to, exacerbation or worsening of troublesome dyskinesia, other problematic dopaminergic symptoms, or other tolerability concerns, a dose reduction (from 2- to 1-capsule inhalation per dose) will be permitted. The medical monitor should be contacted, and the investigator should use his/her clinical judgment to determine if an additional unscheduled visit is required and what assessments should be performed (e.g., physical examination, spirometry, etc.).

11. DESCRIPTION OF ASSESSMENTS

11.1. Safety Assessments

Safety will be assessed from physical examination, AE reporting, standard and orthostatic vital signs (BP, RR, and HR), clinical laboratory values (hematology and biochemistry), ECGs, and spirometry and DLco for evaluation of pulmonary function. In addition, UPDRS Part 4, and evaluations for assessing suicidality, somnolence, and impulse control disorders will be done.

11.1.1. Physical Examination

A complete physical examination (head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at the visits specified in Appendix 2 through Appendix 15. Genital, rectal, and breast examination may be excluded if not clinically indicated. Height (cm) and weight (kg) will be assessed at screening by qualified personnel. Physical examinations will be performed by a

physician. In addition, medical history will be recorded at screening, including smoking history, if applicable.

A brief physical exam to verify continued patient eligibility and to follow up any change in medical history will be performed at visits specified in Appendix 2 through Appendix 15. Symptom-driven brief physical examinations will be performed as clinically indicated at any study visit. All changes identified as clinically noteworthy must be recorded as AEs.

11.1.2. Vital Signs

Standard Vital Signs

Vital sign measurements will include RR, BP (systolic [SBP] and diastolic [DBP]), and HR after the patient has rested in a supine or semi-supine position for at least 5 minutes.

Blood pressure must be assessed using an appropriate device, and the arm position must be standardized for each patient using a cuff size that is appropriate for the patient. These measurements are to be taken in the same arm for the duration of the study. The position of the cuff on the arm should be in line with the heart with the arm lying next to the patient when semi-supine and should be in line with the heart at approximately a 45-degree angle from horizontal for the standing measurements. "Standard" BP and HR measurements should be taken after resting in a supine or semi-supine position for at least 5 minutes.

Respiratory rate should be recorded for 30 seconds, and the value multiplied by 2 for the rate per minute.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. If out-of-range BP, RR, or HR results are observed, the assessments may be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

Orthostatic Vital Signs

At screening (SV1 or SV2) and at each subsequent study visit and in the event of a clinically significant finding that could be suggestive of symptomatic orthostatic hypotension (e.g., dizziness, lightheadedness, or other AE), orthostatic vital signs will be performed. During the orthostatic vital signs assessment, at least one other staff member familiar with the study (not measuring vital signs) must be present should symptoms or an AE occur.

In order to obtain orthostatic vital signs, patients should undergo the following procedures in sequential order:

1. After the supine/semi-supine BP and HR measurements have been done, the patient will be asked to sit on the edge of the bed/table with feet on the floor (or with feet dangling from the bed/tableside depending on the height of the bed/table) for approximately 30 seconds.
2. The person performing the assessment will then ask the question, "Are you ready to stand?"
    - If the patient responds in the affirmative, the patient will proceed to stand and then be asked to remain standing for 2 minutes. After standing for 2 minutes, BP and HR will be recorded.

- If the patient states that he or she is not ready to stand, the patient will be allowed to sit as positioned for 1 additional minute and will be asked again if they are ready to stand. The patient will proceed to stand. After standing for 2 minutes, one measurement will be taken for BP and HR.
- If the individual is still unable to stand, vital signs will be measured while the patient is in an upright seated position.

Orthostatic hypotension will be defined as a reduction in SBP of 20 mmHg or more, and/or a reduction in DBP of 10 mmHg or more, for the standing measurement compared to the semi-supine measurement. If orthostatic hypotension is suspected, the measurement process may be repeated at the investigator's discretion. Any changes of potential clinical concern will be recorded as AEs.

11.1.3. Electrocardiogram

Standard 12-lead ECGs will be obtained after the patient has rested in a supine position for at least 5 minutes. Electrocardiograms will be measured using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, QT interval corrected using Bazett's formula (QTcB) and QT interval corrected using Fridericia's formula (QTcF).

Please refer to Appendix 2 through Appendix 15 regarding specific times of ECG assessments at individual study visits.

Electrocardiogram equipment will be provided to each study site to perform all assessments.

Electrocardiograms will be repeated if clinically significant abnormalities are observed or artifacts are present. Electrocardiograms will be reviewed by qualified staff and over-read by the Central ECG Laboratory.

11.1.4. Laboratory Parameters

Hematology, clinical chemistry, and additional laboratory parameters to be tested are listed in Appendix 17. Patients do not need to be in a fasted state at the time of any laboratory sample; however, fasted status will be documented (with fasting defined as at least 4 hours following the last meal or snack).

Laboratory samples will be analyzed by a central laboratory (ACM Global Central Laboratory) to ensure consistent interpretation of results. In the event of an unexplained clinically significant abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

11.1.5. Pregnancy Status

Women of child-bearing potential must have a negative pregnancy test (serum hCG test) at screening. A serum hCG test will be performed at screening (SV1 or SV2) and at TV/OV1, TV/OV3, TV/OV4, TV/OV5, and TV/OV6, if applicable.

If sexually active and the female is of child-bearing potential, the patient (and his/her partner) should use adequate contraceptive measures for the duration of the study. Adequate measures should consist of 2 forms of contraception (except in cases of surgical sterilization), at least 1 of which must be a barrier method (e.g., male partner uses condoms, plus female partner uses

diaphragm and spermicidal gel, or cervical cap and spermicidal gel, or intrauterine device, or oral contraceptive pill).

Female patients found to be pregnant will be withdrawn from further treatment, but will be followed for the duration of their pregnancy.

11.1.6. Spirometry

The following is a description of the pulmonary function testing at clinical sites:

Pulmonary function will be measured by spirometry using the guideline specified by the Third National Health and Nutrition Examination Survey (NHANES III) (Hankinson 1999). Spirometry (with the exception of spirometry being performed in conjunction with DLco) will be performed by trained and qualified staff at each study site. Spirometry data will be reviewed by a central spirometry laboratory (Biomedical Systems, Inc.) which will provide a quality over-read of all evaluations based on acceptability and repeatability metrics in accordance with ATS criteria (Miller et al., 2005). FEV1, FVC and FEV1/FVC ratio will be recorded from the single "best test" (based on effort with highest summed FEV1 and FVC). Variables and comparisons will include the actual and expected forced FEV1, FVC, and FEV1/FVC ratio. Patients with FEV1 <50% of predicted for race, age, sex, and height, or FEV1/FVC ratio ≤60% in the ON state at screening will be excluded from the study. A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% at screening in order to determine eligibility. All patients with an FEV1/FVC ratio that is >60% to <70% at screening will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/ERS criteria. The results of the bronchodilator challenge will be reviewed by a pulmonologist. Any subject requiring pulmonary adjudication at screening will not be randomized until after full pulmonologist review and approval.

Spirometry assessments will be done at the time points indicated in Appendix 2 through Appendix 15. The patient's motor state at the time of each spirometry assessment will be recorded. At SV1, spirometry assessments should be done while the patient is in both the ON and OFF states. At SV2, spirometry assessments will be done only if a repeat measurement is needed for assessing eligibility.

Spirometry equipment will be provided to each study site to perform all spirometry assessments.

11.1.7. Carbon Monoxide Diffusing Capacity

Patients will undergo diffusing capacity of the lungs for carbon monoxide (DLco) assessments, which will be performed in accordance with ATS criteria (Miller et al., 2005), at a dedicated pulmonary function facility after SV2 (and prior to TV/OV1), within 2 weeks prior to TV/OV3, TV/OV4, TV/OV5, and TV/OV6, and at 4 to 5 weeks after TV/OV6, as described in the Appendix 2 through Appendix 15. These assessments should be performed while the patient is in the ON state (as reported by the patient to the pulmonary technician). Trained and qualified pulmonary function facility technicians will perform a slow vital capacity maneuver, followed by DLco, and then spirometry.

DLco and slow vital capacity maneuvers will be assessed and processed in accordance with ATS/ERS standards. Spirometry procedures will be conducted at the same visits in the same manner as those conducted at clinical sites in accordance with ATS criteria (see Section 11.1.6). All DLco data collected at pulmonary function labs will be sent to and reviewed by a central Pulmonary Function Testing reviewer (TechEd Consultants).

11.1.8. Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at the start of the study, worsens during the study, regardless of the suspected cause of the event. Changes in conditions present at screening and new symptoms, physical signs, syndromes, or diseases should be noted on the AE page of the eCRF during the study. Any AEs reported prior to the first study treatment (or TV/OV1) will be considered baseline AEs, and AEs reported from first treatment (or TV/OV1) will be considered treatment-emergent adverse events (TEAEs).

AEs may be volunteered spontaneously by the patient, discovered as a result of general questioning by the study staff, or determined by physical examination. At each visit, the patient will be asked, "Have you experienced any problems since your last visit?" All AEs will be recorded on the eCRF. For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology rather than the patient's own words. Each AE will also be described in terms of duration, frequency, intensity, association with the study medication, assessment of possible causes, actions taken, and outcome, using choices given on the eCRF. Specific guidelines for classifying AEs by intensity and relationship to study medication are given in Table 3 and Table 4, respectively.

Table 3 Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 4 Classification of Adverse Events by Relationship to Study Medication

Definitely not related: The AE is definitely not related to the drug. This designation should be reserved for those events which occur prior to study treatment or for those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident as a passenger).
Unlikely related: There is no reasonable association between the study treatment and the suspected event and the event could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Possibly related: The suspected adverse event may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the patient's clinical state or by other modes of therapy concomitantly administered to the patient.
Probably related: The suspected adverse event follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state.
Definitely related: This designation should be reserved for those events which have no uncertainty in their relationship to treatment administration.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

11.1.9. Serious Adverse Events

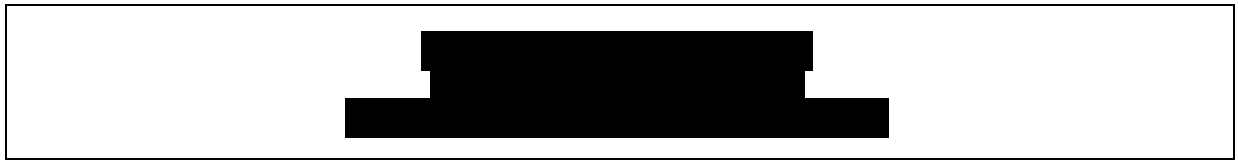
A serious adverse event (SAE) is defined as any AE that meets 1 or more of the following criteria:

- The event results in death.
- The event is life-threatening.
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization.
- The event is a congenital anomaly.
- The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

A serious AE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as a serious AE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: for example, nausea of several hours' duration may be rated as severe but may not be considered serious.

An SAE occurring during the study or within 4 weeks of stopping the treatment must be reported to the [redacted] and will be communicated to the Sponsor. **Any such SAE due to any cause, whether or not related to the study medication, must be reported within**

24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using the following fax or email address for the [redacted]:



The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the [redacted] within 10 calendar days. All SAEs will be followed until the investigator and Sponsor agree the event is satisfactorily resolved.

11.1.10. Suspected Unexpected Serious Adverse Reactions

Adverse events which meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and will be reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., is not consistent with the applicable product information such as the Investigator's Brochure for an unapproved investigational product or summary of product characteristics or product insert for an authorized product)
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product.

It is the Sponsor's responsibility to report SUSARs to the IRBs, IECs, and regulatory agencies in each country, although this responsibility may be delegated to the contract research organization (CRO). The procedures for notifying the health authorities and the IRBs/IECs of all SAEs/SUSARs (as appropriate) will be documented in the CRO study-specific and Sponsor standard operating procedure (SOP). SUSARs will be reported to the appropriate health authorities within 7 or 15 days (as appropriate).

11.1.11. Other Significant Adverse Events

To ensure patient safety, the investigator should also notify the medical monitor should any AE occur that is considered significant but does not meet criteria for an SAE, or that is considered unexpected. An unexpected AE is an AE that is not identified in nature, intensity, or frequency in the investigational drug brochure. The medical monitor and/or Sponsor may then choose to discontinue the patient from the study. In addition, any field monitor who notes a significant AE

or medical condition while reviewing the eCRFs or source documents at the site must immediately convey this information to the medical monitor.

11.1.12. Other Safety Assessments

11.1.12.1. UPDRS Part 4 (CVT-301 Treatment Group) and Examiner-Rated Dyskinesia

The UPDRS Part 4 is an assessment of potential complications of PD therapies. Questions 32-35 (related to dyskinesias) and 36-39 (related to clinical fluctuations) only will be completed for the CVT-301 patients as indicated in the time and events tables in Appendix 2 through Appendix 15.

Additionally, during the post-dosing follow-up period at TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6, observe the patient for the appearance of dyskinesia, and note in the eCRF if the patient experiences dyskinesia within the 60-minute post-dose period. If applicable, record the maximum severity of any dyskinesia during the 60-minute post-dose period. The examiner will also note if the patient converts to the ON state during the 60-minute post-dose period and if so, whether the patient is still in the ON state at 60 minutes post-dose.

11.1.12.2. Columbia-Suicidality Severity Rating Scale

The C-SSRS is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. An initial baseline version will be given at TV/OV1, and a "since last visit" version will be given at all treatment visits to detect any emergence of suicidal ideation or behavior. The clinic staff should address any emerging neuropsychiatric needs in the event that the C-SSRS indicates active suicidal ideation.

11.1.12.3. Epworth Sleepiness Scale

The Epworth Sleepiness Scale is used to determine the level of daytime sleepiness. There are 8 situations listed (e.g., sitting and reading, watching television) for which patients rate their likelihood of dozing or sleeping (0=would never doze or sleep, 1=slight chance of dozing or sleeping, 2=moderate chance of dozing or sleeping, and 3=high chance of dozing or sleeping). A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy. The baseline assessment will be completed at TV/OV1 of this study. As described in the time and events tables in Appendix 2 through Appendix 15, additional assessments will be completed at TV/OV4 and TV/OV6.

11.1.12.4. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

The QUIP is an instrument used to measure the extent of impulsive and compulsive behaviors in PD patients. The QUIP has 3 sections: Section 1 assesses gambling, sexual, buying, and eating disorders; Section 2 assesses other compulsive behaviors (punding, hobbyism, and walkabout); and Section 3 assesses compulsive medication use. The baseline assessment will be completed at TV/OV1 of this study. As described in the time and events tables in Appendix 2 through Appendix 15, additional assessments will be completed at TV/OV4 and TV/OV6.

11.2. Exploratory Efficacy Assessments

Exploratory efficacy will be evaluated primarily for the CVT-301-treated patients. Exploratory fficacy will be evaluated from both in-clinic, at-home assessments, and patient-reported assessments as outlined by the criteria below. A limited number of patient-reported assessments identified in the subsections below (i.e., the PDQ-39, UPDRS Part 2, and S&E ADL) will also be performed in the observational cohort.

In-Clinic Criteria:

- UPDRS Part 3 motor score
- Occurrence of an ON state during the 60-minute post-dose period and if an ON state occurs during the 60-minute post-dose, whether or not the patient is still in the ON state at 60 minutes post-dose

At-Home Criteria and/or Patient-Reported Assessments:

- Total daily OFF time at home, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, based on the PD Diary.
- PDQ-39
- PGI-C
- S&E ADL
- UPDRS Part 2

11.2.1. Assessment of ON and OFF States and Dyskinesia (CVT-301 Treatment Group)

An "OFF state" is defined as the time when medication is not providing benefit with respect to mobility, slowness, and stiffness. OFF episodes may be heralded by non-motor symptoms (e.g., pain, anxiety) prior to the appearance of motor symptoms.

An "ON state" is defined as the time when medication is providing benefit with respect to mobility, slowness, and stiffness, and may or may not be providing complete alleviation of all PD symptoms.

For recording motor state in the PD Diary, when patients are in an ON state, the presence and extent of dyskinesia (involuntary twisting, turning movements that are an effect of medication) will also be noted:

- ON with no dyskinesia
- ON with non-troublesome dyskinesia (ON with dyskinesia that does not interfere with function or cause meaningful discomfort)
- ON with troublesome dyskinesia (ON with dyskinesia that interferes with function or causes meaningful discomfort)

These ON and OFF definitions are to be used in training the patients to recognize and record their ON and OFF states. Patients will record their ON and OFF states in their diaries at home.

11.2.1.1. In-Clinic Assessments (CVT-301 Treatment Group)

See Section 11.1.12.1.

11.2.1.2. At-Home Assessments

11.2.1.2.1. PD Diary

During the 3 consecutive days prior to SV2 and TV/OV1, TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6, patients in the CVT-301 treatment group will record their waking ON/OFF status (time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia) and time asleep in the PD Diary (also referred to as the PD Home Diary or "Hauser diary") (Hauser 2000).

Patients in the observational cohort will complete the PD Diary for 3 consecutive days prior to SV2 and TV/OV1, but will not be required to complete the PD Diary for the remainder of the study.

New diaries will be distributed to appropriate patients at each study visit, except for TV/OV6, and patients will bring the completed diaries to the following clinic visit. Information in the diaries will be reviewed, signed, and dated by clinic staff.

11.2.1.2.2. Screening ON/OFF Episodes Log (for the Screening Period)

All patients will record the discrete number of OFF episodes experienced by the patient during their waking day in the Screening ON/OFF Episodes Log for the 3 consecutive days prior to SV2 and TV/OV1. These logs will be distributed at SV1 and SV2, and patients will bring the completed logs to the clinic at SV2 and TV/OV1. Information in the logs will be reviewed, signed, and dated by clinic staff.

11.2.1.2.3. Inhaled Dosing Log (for the Treatment Period) for CVT-301 Treatment Group

Every day during the treatment period, patients in the CVT-301 treatment group will record the number of times the inhaler was used and the number of capsules used for each inhalation treatment. New logs will be distributed at TV/OV1, TV/OV2, TV/OV3, TV/OV4, and TV/OV5, and patients will bring the completed logs to the clinic at TV/OV2, TV/OV3, TV/OV4, TV/OV5, and TV/OV6. Information in the logs will be reviewed and recorded by clinic staff.

11.2.2. UPDRS Part 3 (CVT-301 Treatment Group)

The UPDRS Part 3 is the motor section of the UPDRS examination, given by interview with actions by the patient. Some questions require multiple ratings to be assigned to each extremity. The areas addressed by this exam include speech, facial expression, tremor at rest, postural tremor, rigidity, finger taps, hand movements, rapid alternating movement (hands), leg agility, arising from a chair, posture, gait, postural stability, and body bradykinesia/ hypokinesia.

The UPDRS Part 3 will be assessed at screening in both ON and OFF states to familiarize the patient with the study evaluations as well as to document each patient's response to his/her own PD medications; to enter the study, the difference between UPDRS Part 3 scores in the ON and OFF states must be ≥25%.

The percent difference is calculated as follows:

([UPDRS III value in OFF state] – [UPDRS III value in ON state])/ UPDRS III value in OFF state

The UPDRS Part 3 assessments will be done for the CVT-301 patients at TV/OV2, TV/OV3, TV/OV4, TV/OV5 and TV/OV6, immediately before and at various time points after study medication dosing, as indicated in the time and events tables in Appendix 2 through Appendix 15.

11.2.3. PDQ-39

The PDQ-39 is a self-report questionnaire that covers 8 aspects of quality of life: mobility, activities of daily living, emotions, stigma, social support, cognitions, communication, and bodily discomfort. Scores are reported for each of the 8 quality of life scales and for the total of all 39 items.

The PDQ-39 will be completed upon arrival for patients assigned to the CVT-301 treatment group and the observational cohort as indicated in the time and events tables in Appendix 2 through Appendix 15.

11.2.4. PGI-C (CVT-301 Treatment Group)

For this study, the PGI-C is a 7-point scale that requires the patient to rate their overall condition with regard to PD by answering the following question: **How has the addition of study drug changed your Parkinson's disease?** This change is rated as 1 = much improved; 2 = improved; 3 = a little improved; 4 = no change; 5 = a little worse; 6 = worse; or 7 = much worse. If the assessment is not done, then the score is marked as 0; any values of zero are not included in any analyses and thus are treated as missing.

The PGI-C scale will be completed by the patients in the CVT-301 treatment group as indicated in the time and events tables in Appendix 2 through Appendix 15.

11.2.5. Schwab & England Activities of Daily Living

The S&E ADL scale will be completed by a qualified rater upon arrival for patients assigned to the CVT-301 treatment group and the observational cohort as indicated in the time and events tables in Appendix 2 through Appendix 15, preferably while the patient is in the ON state.

11.2.6. UPDRS Part 2

The UPDRS Part 2 is an evaluation of the ADL; this will be completed by a qualified rater upon arrival for patients assigned to the CVT-301 treatment group and the observational cohort as indicated in the time and events tables in Appendix 2 through Appendix 15, preferably while the patient is in the ON state.

11.3. Other Assessments Used for Baseline Disease Characteristics for all Patients

Patients' PD diagnosis will be documented by the UK Brain Bank criteria, and PD severity will be staged using the modified Hoehn and Yahr disease severity scale. The MMSE is used to assess the patient's cognitive state.

11.3.1. UK Brain Bank Criteria

Steps 1 and 2 of the UK Brain Bank criteria will be used to confirm the patient's PD diagnosis. Step 1 requires that the patient have certain signs and symptoms of Parkinsonian syndrome, and Step 2 lists exclusion criteria that the patient must not have to be diagnosed with PD. The UK Brain Bank criteria are presented in Appendix 18 and discussed in Hughes (1992).

11.3.2. Modified Hoehn and Yahr PD Severity Scale Assessment

PD severity will be staged using the modified Hoehn and Yahr disease severity scale (refer to Appendix 19).

11.3.3. MMSE

The MMSE is a brief, 30-point test used to screen for cognitive impairment. The categories tested include orientation to time, orientation to place, registration, attention and calculation, recall, language, repetition, and complex commands. Any score ≥25 points is considered normal. Scores below 25 can indicate mild (21-24 points), moderate (10-20), or severe (0-9) cognitive impairment.

11.3.4. Pulmonary Function Baseline Questionnaire

The patient's pulmonary history will be recorded by completing the Pulmonary Function Baseline Questionnaire at screening. Site staff will administer the Pulmonary Function Baseline Questionnaire to all patients. The questionnaire includes sections for recording asthma, COPD, and other lung or airway disease symptom history. There is also a section for recording patient-reported instances of current pulmonary symptomology.

11.4. Appropriateness of Measurements

All safety assessments to be used in this study are commonly used, standard measurements frequently seen in PD studies and/or pulmonary studies. The modified Hoehn and Yahr disease severity scale is a validated method of assessing the severity of PD, and the UPDRS Part 3 is a validated tool measuring the motor aspects of a PD patient. The UPDRS Part 2, UPDRS Part 4, and S&E ADL rating scales are also standard tools for the assessment of PD patients. Rater training in UPDRS Part 2, UPDRS Part 3, UPDRS Part 4, S&E ADL and C-SSRS scales will be given to clinic staff members who plan to administer the tests. The PDQ-39 is a validated quality of life measure for PD patients. The PGI-C scale is a tool for assessing patient-perceived changes in their overall disease condition. The PD Diary to be used in this study (also referred to as the Hauser diary) has been validated for use in PD patients as a tool to assess patient-defined clinical status at home over a period of time (recording daily OFF time, ON time, and time with non-troublesome and troublesome dyskinesia).

12. DATA MANAGEMENT AND STATISTICAL ANALYSIS

Completed eCRFs for this study will be entered by electronic data capture (EDC) into the study database. The statistical analysis of these data will be performed by the Sponsor or its representative. The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.3 or higher (SAS Institute, Cary, NC). All data will be listed, and

summary tables will be provided. Summary statistics will be presented by treatment group (when applicable).

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in the statistical analysis plan (SAP), which will give a detailed technical description of all statistical analyses. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

12.1. Determination of Sample Size

Approximately 250 CVT-301 treatment patients and 115 control patients will be enrolled in this study. It is assumed that the drop-out rate will be approximately 25%.

Assuming that there is no difference in the changes from baseline between the CVT-301-treated patients and the observational cohort in regards to FEV1, the study has the following power for the comparison between the 2 groups. The upper limit of the 95% confidence interval for the difference between the 2 groups in change from baseline in FEV1 will be less than 0.121 L with 90% power, assuming 188 and 86 patients completing the study in the CVT-301 treatment group and observational cohort, respectively.

12.2. Study Populations

All patients who are enrolled in CVT-301-005 and receive at least 1 dose of CVT-301 will be included in the safety population. The patients in the observational cohort will be included in the analyses if they provide any data after TV/OV1.

12.3. Definition of Baseline

In all statistical analyses of the CVT-301 treatment group, the visit at which the CVT-301 treatment was initiated will be used as the baseline. However, for all patients who were included in the CVT-301-002 or CVT-301-003 studies, TV/OV1 of the CVT-301-005 study will be used as baseline. For the observational cohort, the assessments at TV/OV1 will be used as baseline.

12.4. Background and Demographic Characteristics

Demographics and baseline characteristics will be summarized descriptively for patients treated with CVT-301 and for the patients in the observational cohort. In addition to the total CVT-301 group, the data from the CVT-301 naïve patients who are enrolled in this study and from the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies will be summarized separately. At least the following variables will be summarized:

- Demographics (age, gender, race, height, weight)
- Smoking history (current, former, never: pack-years for current and former smoker)
- History of PD (UK Brain Bank criteria, time since diagnosis of PD, duration of LD treatment)

- LD treatment at baseline (total daily dose, dosing frequency, decarboxylase inhibitor [CD or benserazide], use of standard/quick/controlled release LD, use of COMT inhibitor)
- Other antiparkinsonian treatment at baseline (use of dopamine agonists, MAO-B inhibitors, anticholinergics, amantadine, or other treatment)
- Disease severity (modified Hoehn and Yahr stage [in the ON state], UPDRS Part 3 at screening)
- Cognitive status (MMSE)
- Average daily number of OFF episodes experienced (determined from Screening ON/OFF Episodes and Treatment Log.

12.5. Safety Analysis

The disposition of the patients will be summarized by tabulating the number of screened, randomized, completed, and discontinued patients. The reasons for premature discontinuations will be tabulated.

The extent of exposure to study treatment will be summarized for the patients who received CVT-301 treatment. The time period between TV/OV1 and TV/OV6 (or Early Withdrawal Visit) will be used as the measure of extent of exposure for the patients randomized to the observational cohort. Adverse events will be tabulated by treatment group according to the Medical Dictionary for Regulatory Activities (MedDRA). Study-emergent and treatment-emergent adverse events (TEAEs) will be summarized by body system and preferred term. For patients in the observational cohort, the AEs collected between TV/OV1 and TV/OV6 (or Early Withdrawal Visit) will be considered as TEAEs. Furthermore, the time of onset of the TEAEs will be summarized.

For vital signs, ECG parameters, spirometry measurements, and DLco, the changes from pre-dose to post-dose assessments of the corresponding day will be calculated and described using descriptive statistics. For spirometry, DLco, and safety laboratory variables, the differences in pre-dose values between the study days will be described. Furthermore, the changes in the spirometry values and difference between the groups will be estimated using a Mixed Model for Repeated Measurements (MMRM) similar to the one used for the efficacy variables. The proportion of patients with abnormal spirometry values will be tabulated using different criteria for the threshold (e.g., at least 10% or 20% change from baseline at any single visit, at least 10% or 20% change from baseline on at least 2 consecutive visits). The proportions of patients meeting ATS quality criteria (and also for those ‘rejected’) will be summarized. All spirometry analyses will be performed both for all patients regardless of the ATS quality criteria and separately excluding the assessments not meeting the ATS quality criteria.

At least the following variables will be analyzed:

- Vital signs: standard and orthostatic systolic and diastolic BP and HR.
- ECG: HR, PR, QRS, QT and RR intervals, QTcB (Bazett's correction formula calculated as $QT/RR^{1/2}$) and QTcF (Fridericia's correction formula calculated as

$QT/RR^{1/3}$). ECG parameter values or parameter changes of potential clinical concern will be tabulated.

- Spirometry: FEV1, FVC, and the FEV1/FVC ratio during specified treatment visits and over the course of the study will be evaluated. The number and proportion of patients with pre-specified changes in spirometry parameters will be tabulated.

Changes from baseline to follow-up in the rating scales for assessing suicidality, somnolence, and impulse control disorders will be summarized descriptively.

12.5.1. Interim Safety Data Review

Safety data will be reviewed by a DSMC that will include relevant medical experts (including a neurologist and pulmonologist), an independent statistician, and additional representatives (as will be defined in the DSMC Charter). Safety data, including but not limited to AEs, spirometry, vital signs, and ECG data will be reviewed. The safety review will be documented in a DSMC Charter prior to the start of the study. In the event that potential safety issues are identified, the committee may recommend modification of the study design or study termination, which will be communicated promptly with investigators, IRBs, IECs, and regulatory agencies, in accordance with legal and regulatory requirements. Interim analyses, which will not affect study conduct, may be performed to support regulatory submissions. These analyses will be described in the SAP.

12.6. Exploratory Efficacy Analysis

The derivation of the exploratory efficacy variables will be defined in detail in the SAP.

The changes from baseline in continuous exploratory efficacy variables will be estimated using an MMRM. The model will include visit and the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) as fixed factors. The baseline value will be used as a covariate. For variables which do not have a pre-treatment baseline assessment, OFF-state baseline UPDRS Part 3 score will be used as the baseline covariate. An unstructured covariance structure will be applied for the MMRM. In case the model will not converge with the unstructured covariance structure, compound symmetry will be used instead.

The sensitivity analyses will be specified in the SAP. Sensitivity analysis will be performed at least for the method to handle missing data (e.g., last observation carried forward, pattern mixture model using multiple imputation instead of MMRM), definition of analysis population (e.g., patients completing the study instead of observed cases), and statistical method (e.g., analysis of covariance [ANCOVA] models separately for each visit instead of MMRM).

The categorical data will be primarily evaluated descriptively. Each visit will be evaluated separately for the categorical endpoints.

The exploratory efficacy data collected from the patients in the observational cohort will be summarized with descriptive statistics.

13. STUDY MANAGEMENT

13.1. Approval and Consent

13.1.1. Regulatory Guidelines

The study will be performed under good clinical practice (GCP) in accordance with the guidelines of the International Conference on Harmonisation (ICH), in accordance with United States of America (USA) Investigational New Drug (IND) regulations (21 Code of Federal Regulations [CFR] 312), and the local national laws (as applicable).

13.1.2. Institutional Review Board/Independent Ethic Committees

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms, patient information sheets, and advertising materials. No drug will be shipped to a site until written IRB or IEC authorization has been received by the Sponsor or its representative.

13.1.3. Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The principal investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved informed consent form prior to the start of the study.

13.2. Financing and Insurance

Prior to the trial commencing, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The Sponsor has insurance coverage for trial-related, medicine-induced injury, and other liabilities incurred during clinical trials which will provide compensation for any study-related injury according to the guidelines set out by the Association of the British Pharmaceutical Industry, namely “Clinical Trials Compensation for Medicine Induced Injury.” The Sponsor will provide local country-specific insurance, as required.

13.3. Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation, clinical supplies, and study medication pertaining to the study must be returned to the Sponsor or its representative.

13.4. Study Documentation

By signing a copy of country-specific regulatory forms, the principal investigator acknowledges that he/she has received a copy of the investigational drug brochure on CVT-301 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in the country-specific forms. No changes in this protocol can be made without the Sponsor's written approval.

The investigator (CRO, if applicable) will supply the Sponsor with the following documents:

- Original, signed Food and Drug Administration (FDA) Form 1572 and other country-specific forms
- Original signed FDA financial disclosure forms
- Curricula vitae for all investigators listed on country-specific forms
- Copy of principal investigator's medical licensure/medical registration number
- Signed protocol signature page
- List of IRB/IEC members and their occupations/affiliations or multiple assurance number
- Letter indicating IRB/IEC approval to conduct the protocol
- Copy of IRB/IEC-approved informed consent form
- The Sponsor will supply the investigator with the following documents:
- Clinical study protocol
- Investigational drug brochure
- Sample informed consent form
- Case report forms/ instruction manual
- Insurance letter

13.5. Data Handling

Any data to be recorded directly in the eCRF (to be considered as source data) will be identified at the start of the trial.

Accurate and reliable data collection will be assured by 100% verification and cross-check of the eCRFs against the investigator's records by the study monitor. A comprehensive validation check program will verify the data, and queries will be generated for resolution by the investigator. During monitoring visits, the monitor will also generate data queries via the eCRF system for resolution by the investigator.

13.6. Study Monitoring and Auditing

This study will be monitored at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of GCP. On-site review of eCRFs will include a review for

completeness and clarity, and consistency with source documents available for each patient. Note that a variety of original documents, data, and records may be considered as source documents in this trial.

Medical advisors and clinical research associates or assistants may request to witness patient evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor, by the CRO, or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required patient records. By signing this protocol, the investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

13.7. Retention of Records

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 [HIPAA] Privacy Regulation) or equivalent. The investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

13.8. Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

13.9. Publication

As a multicenter trial, the Sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the Sponsor will submit draft manuscripts to an assigned authorship committee for their comments. In conformity with the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors, investigators whose contribution consists solely in the collection of data will not be named individually as authors (Kassirer 1991). Rather, those investigators will receive a collective authorship as the "CVT-301 Study Group" and will be identified in a note.

Individual investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the Sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation prior to its submission. This review is required to ensure that the Sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

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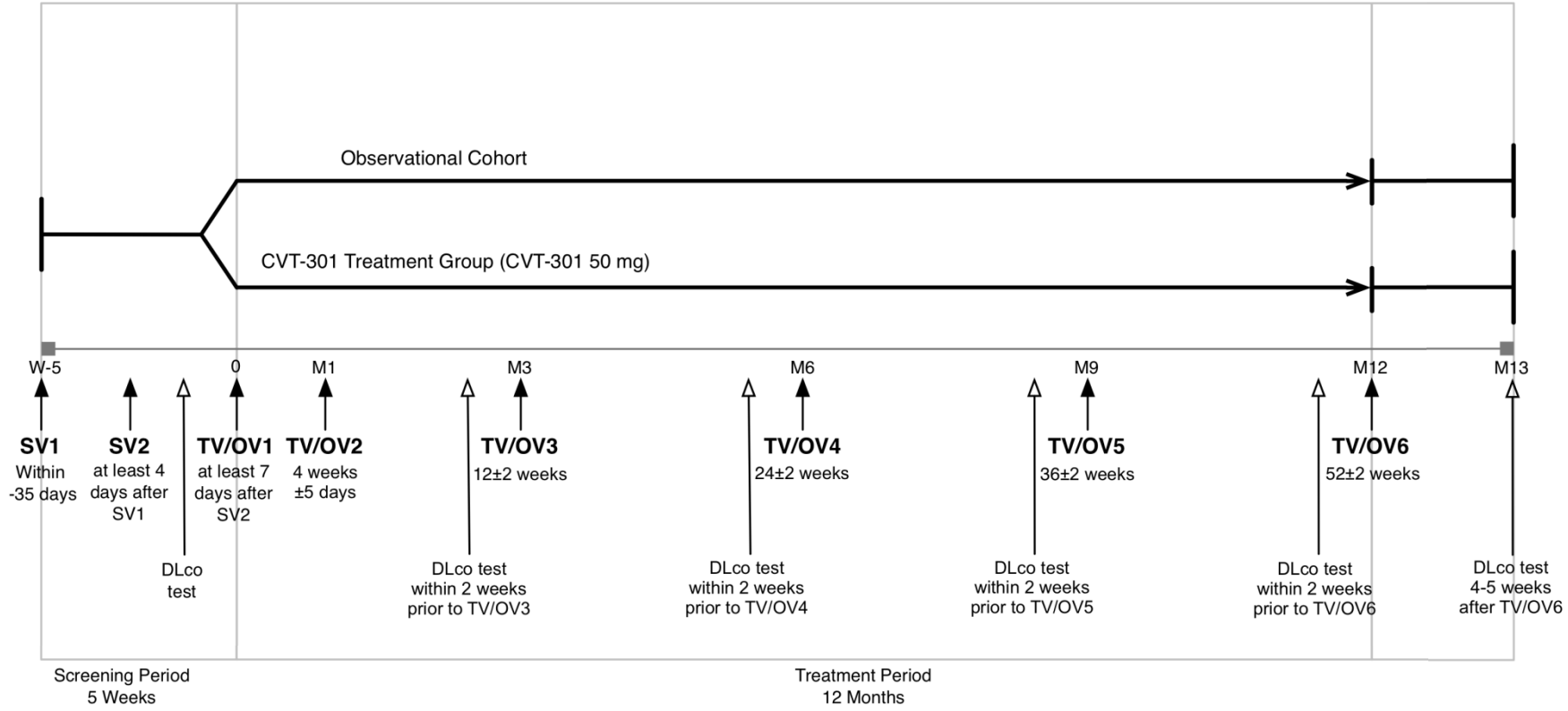
15. APPENDICES – TABLE OF CONTENTS

APPENDIX 1: OVERALL VISIT SCHEDULE SCHEMATIC



Abbreviations: DLco = carbon monoxide diffusing capacity; M = month; SV = screening visit; TV/OV = Treatment Visit/Observational Visit; W = weeks.

APPENDIX 2: TIME AND EVENTS TABLE—SCREENING VISIT 1 (SV1) (WITHIN 35 DAYS PRIOR TO TV/OV1)

Procedures[1]	At arrival (assess in ON or OFF state)	Assess in ON state[2]	Assess in OFF state	End of SV1	Post-SV1 Telephone Contact
Consent	X				
Eligibility according to inclusion/exclusion criteria	X				
Medical history including PD history and smoking history	X				
Confirm PD diagnosis and severity (UK Brain Bank/Modified Hoehn and Yahr scale)		X			
Record average number of OFF hours during waking	X				
PD medications (confirm as stable)	X				
Concomitant medications	X				
MMSE		X			
Physical examination (full)	X				
Pulmonary Function Baseline Questionnaire	X				
Electrocardiogram	X				
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X				
Spirometry		X	X		
UPDRS Part 3		X	X		
Patient training on self-report of ON/OFF states		X	X		
ON/OFF concordance testing		X	X		
Inhaler training using sham capsules		X	X		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[3]				
Distribute PD Diary and Screening ON/OFF Episodes Log and review instructions for completion[4]				X	
Monitor for AEs		X			
Schedule next visit				X	
Post-SV1 telephone contact: call patient ~4 days prior to SV2					X

[1]Procedures appear in the table in the suggested order of completion.
[2]If patient arrives in OFF state, perform OFF assessments first, then have patient take next regularly scheduled dose of PD meds and complete ON assessments.
[3]Document whether patient is fasting (≥4 hours after last snack or meal).
[4]The PD Diary and Screening ON/OFF Episodes Log are to be completed for the 3 consecutive days prior to SV2.

APPENDIX 3: TIME AND EVENTS TABLE—SCREENING VISIT 2 (SV2) (AT LEAST 4 DAYS AFTER SV1)

Procedures[1]	**At arrival (assess in ON or OFF state)**	**Assess in ON state**	**Assess in OFF state**	**End of SV2**	**Post-SV2 Telephone Contact**
Confirm eligibility through review of complete PD Diary and Screening ON/OFF Episodes Log[2]	X				
Record any changes in usual PD medication dose/regimen	X				
Record any changes in concomitant medications	X				
Inhaler training using sham capsules and IFU[3]		X	X		
Patient training on assessment of ON/OFF state		X	X		
Distribute PD Diary and Screening ON/OFF Episodes Log and review instructions for completion[4]				X	
Monitor for AEs	X				
Schedule DLco assessment (to be completed prior to TV/OV1) and next visit				X	
Post-SV2 telephone contact: call patient 4 to 6 days prior to TV/OV1					X
Screening procedures from SV1 that can be completed/repeated at SV2, if necessary:	**At arrival (assess in ON or OFF state)**	**Assess in ON state**	**Assess in OFF state**		
MMSE		X			
Physical examination (full)	X				
Electrocardiogram	X				
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X				
Spirometry		X	X		
UPDRS Part 3		X	X		
ON/OFF concordance testing		X	X		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[5]				

[1]Procedures appear in the table in the preferred order of completion.
[2]Refer to Section 10.1.2 of protocol for management of incorrect or incomplete patient diaries.
[3]If the patient has undergone inhaler training in both the ON and OFF states at SV1, it may be done in either state at this visit.
[4]The PD Diary and Screening ON/OFF Episodes Log are to be completed for the 3 consecutive days prior to TV/OV1.
[5]Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 4: TIME AND EVENTS TABLE—TREATMENT VISIT 1 (TV1) (AT LEAST 7 DAYS AFTER SV2)

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	15 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV1	Post-TV1 Telephone Contacts
Collect, review, sign, and date Screening ON/OFF Episodes Log and PD Diary	X									
Confirm DLco assessment[2] has been completed prior to visit; if DLco not done, the study visit must be re-scheduled	X									X
Record time of patient's prior usual PD medication dose	X									
Record any changes in usual PD medication dose/regimen	X									
Concomitant medications	X									
PDQ-39 (in ON state)	X									
Physical examination (brief)	X									
UPDRS Part 2 (preferably in ON state)	X									
S&E ADL (preferably in ON state)	X									
UPDRS Part 4 (Questions 32-35 and 36-39)	X									
Electrocardiogram	X[3]									
Standard and orthostatic BP and HR	X[3]					X		X		
Respiratory rate	X[3]			X		X	X	X		
Spirometry	X[4]	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[3,5]									
C-SSRS	X[3]									
Epworth sleepiness scale	X[3]									
QUIP	X[3]									
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion	X[6]									
Distribute study drug kits	X									
Review inhaler training	X									
Self-administration of study drug			X[1]							
Monitor for AEs	X									
Schedule next visit									X	
Post-TV1 telephone contact: call patient 1-3 days after TV1										X

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	15 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV1	Post-TV1 Telephone Contacts
Post-TV1 telephone contact: call patient 2 weeks (± 3 days) before TV2										X

[1]First dose of study medication occurs preferably between 2 and 5 hours after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2] DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Procedures can be done at any point after arrival but must be completed before dosing.
[4]Preferably in the ON state.
[5]Document whether patient is fasting (≥4 hours after last snack or meal).
[6]The PD Diary is to be completed for the 3 consecutive days prior to TV2; the Inhaled Dosing Log is to be completed daily through TV6.

APPENDIX 5: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 1 (OV1) (AT LEAST 7 DAYS AFTER SV2)

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV1	Post- OV1 Telephone Contact
Collect, review, sign, and date Screening ON/OFF Episodes Log and PD Diary	X		
Confirm DLco assessment[1] has been performed prior to visit; and if not complete, re-schedule study visit	X		X
Record any changes in usual PD medication dose/regimen	X		
Concomitant medications	X		
PDQ-39 (in ON state)	X (ON)		
UPDRS Part 2 (preferably in ON state)	X (ON)		
S&E ADL (preferably in ON state)	X (ON)		
Physical examination (brief)	X		
Standard and orthostatic BP and HR	X		
Respiratory rate	X		
Electrocardiogram	X		
Spirometry (preferably in ON state)	X (ON)		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[2]		
C-SSRS	X		
Epworth sleepiness scale	X		
QUIP	X		
Monitor for AEs	X		
Schedule next visit		X	
Post-OV1 telephone contact: call patient 2 weeks (± 3 days) before OV2			X

[1]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[2]Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 6: TIME AND EVENTS TABLE—TREATMENT VISIT 2 (TV2) (1 MONTH [4 WEEKS ±5 DAYS] AFTER TV1)

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV2	Post-TV2 Telephone Contact
Collect, review, sign, and date PD Diary and Inhaled Dosing Log	X								
Collect empty capsules, inhalers, and unused supplies	X								
Record any changes in usual PD medication dose/regimen	X								
Record time of patient's prior usual PD medication dose	X								
Record any changes in concomitant medications	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[3]								
Spirometry (preferably in ON state)	X								
C-SSRS	X								
Distribute study drug kits	X								
Review inhaler training	X								
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion	X[4]								
UPDRS Part 3		X[5]		X	X	X	X		
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule next visit								X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)[2]								X	
Post-TV2 telephone contact: call patient 2 weeks (± 3 days) before TV3									X

[1]Dosing of study medication occurs preferably between 2 and 5 hours after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Assessment can be done at any point after arrival but must be completed before dosing.

[4]The PD Diary is to be completed for the 3 consecutive days prior to TV3; the Inhaled Dosing Log is to be completed daily through TV6.
[5]Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

APPENDIX 7: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 2 (OV2) (1 MONTH [4 WEEKS ±5 DAYS] AFTER OV1)

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV2	Post- OV2 Telephone Contact
Record any changes in usual PD medication dose/regimen	X		
Record any changes in concomitant medications	X		
Physical examination (brief)	X		
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X		
Spirometry (preferably in ON state)	X (ON)		
C-SSRS	X		
Monitor for AEs	X		
Schedule next visit		X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)[1]		X	
Post- OV2 telephone contact: call patient 2 weeks (± 3 days) before OV3			X

[1] DLco to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.

APPENDIX 8: TIME AND EVENTS TABLE—TREATMENT VISIT 3 (TV/OV3) (3 MONTHS [12±2 WEEKS] AFTER TV1)

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV3	Post-TV3 Telephone Contact
Collect, review, sign, and date PD Diary and Inhaled Dosing Log	X								
Collect empty capsules, inhalers, and unused supplies	X								
Confirm DLco assessment[2] has been completed prior to visit; if not done, the study visit must be re-scheduled	X								X
Record any changes in usual PD medication dose/regimen	X								
Record time of patient's prior usual PD medication dose	X								
Record any changes in concomitant medications	X								
PGI-C (preferably in an ON state)	X[3]								
C-SSRS	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[3]								
Electrocardiogram	X								
Spirometry (preferably in ON state)	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[4]								
Distribute study drug kits	X								
Review inhaler training	X								
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion	X[5]								
UPDRS Part 3		X[6]		X	X	X	X		
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule next visit								X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)								X	

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV3	Post-TV3 Telephone Contact
Post-TV3 telephone contact: call patient 2 weeks (± 3 days) before TV4									X

[1]Dosing of study medication occurs at least 1 hour after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2]DLco to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Assessment can be done at any point after arrival but must be completed before dosing.
[4]Document whether patient is fasting (≥4 hours after last snack or meal).
[5]The PD Diary is to be completed for the 3 consecutive days prior to TV4; the Inhaled Dosing Log is to be completed daily through TV6.
[6]Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

APPENDIX 9: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 3 (OV3) (3 MONTHS [12±2 WEEKS] AFTER OV1)

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV3	Post- OV3 Telephone Contact
Confirm DLco assessment[1] has been performed prior to visit; and if not complete, re-schedule study visit	X		X
Record any changes in usual PD medication dose/regimen	X		
Record any changes in concomitant medications	X		
C-SSRS	X		
Physical examination (brief)	X		
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X		
Electrocardiogram	X		
Spirometry (preferably in ON state)	X (ON)		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[2]		
Monitor for AEs	X		
Schedule next visit		X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)		X	
Post- OV3 telephone contact: call patient 2 weeks (± 3 days) before OV4			X

[1]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[2]Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 10: TIME AND EVENTS TABLE—TREATMENT VISIT 4 (TV4) (6 MONTHS [24±2 WEEKS] AFTER TV1)

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV4	Post-TV4 Telephone Contact
Collect, review, sign, and date PD Diary and Inhaled Dosing Log	X								
Collect empty capsules, inhalers, and unused supplies	X								
Confirm DLco assessment[2] has been completed prior to visit; if not done, the study visit must be re-scheduled	X								X
Record any changes in usual PD medication dose/regimen	X								
Record time of patient's prior usual PD medication dose	X								
Record any changes in concomitant medications	X								
PDQ-39 (preferably in ON state)	X[3]								
PGI-C (preferably in ON state)	X[3]								
UPDRS Part 2 (preferably in ON state)	X[3]								
S&E ADL (preferably in ON state)	X[3]								
UPDRS Part 4 (Questions 32-35 and 36-39)	X								
C-SSRS	X								
Epworth Sleepiness Scale	X								
QUIP	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[4]								
Electrocardiogram	X								
Spirometry (preferably in ON state)	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[5]								
Distribute study drug kits	X								
Review inhaler training	X								
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion	X[6]								

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV4	Post-TV4 Telephone Contact
UPDRS Part 3		X[7]		X	X	X	X		
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule next visit								X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)								X	
Post-TV4 telephone contact: call patient 2 weeks (± 3 days) before TV5									X

[1]Dosing of study medication occurs at least 1 hour after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Preferably in the ON state; but these must be performed before any other study evaluation.
[4]Assessment can be done at any point after arrival but must be completed before dosing.
[5]Document whether patient is fasting (≥4 hours after last snack or meal).
[6]The PD Diary is to be completed for the 3 consecutive days prior to TV/OV5; the Inhaled Dosing Log is to be completed daily through TV/OV6.
[7]Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

APPENDIX 11: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 4 (OV4) (6 MONTHS [24±2 WEEKS] AFTER OV1)

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV4	Post- OV4 Telephone Contact
Confirm DLco assessment[1] has been performed prior to visit; and if not complete, re-schedule study visit	X		X
Record any changes in usual PD medication dose/regimen	X		
Record any changes in concomitant medications	X		
PDQ-39 (preferably in ON state)	X (ON)[2]		
UPDRS Part 2 (preferably in ON state)	X (ON)[2]		
S&E ADL (preferably in ON state)	X (ON)[2]		
C-SSRS	X		
Epworth Sleepiness Scale	X		
QUIP	X		
Physical examination (brief)	X		
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X		
Electrocardiogram	X		
Spirometry (preferably in ON state)	X (ON)		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[3]		
Monitor for AEs	X		
Schedule next visit		X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)		X	
Post- OV4 telephone contact: call patient 2 weeks (± 3 days) before OV5			X

[1] DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[2] Preferably in the ON state; but these must be performed before any other study evaluation.
[3] Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 12: TIME AND EVENTS TABLE—TREATMENT VISIT 5 (TV5) (9 MONTHS [36±2 WEEKS] AFTER TV1)

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV5	Post-TV5 Telephone Contact
Collect, review, sign, and date PD Diary and Inhaled Dosing Log	X								
Collect empty capsules, inhalers, and unused supplies	X								
Confirm DLco assessment[2] has been completed prior to visit; if not done, the study visit must be re-scheduled	X								X
Record any changes in usual PD medication dose/regimen	X								
Record time of patient's prior usual PD medication dose	X								
Record any changes in concomitant medications	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[3]								
Spirometry (preferably in ON state)	X								
Clinical laboratory tests (serum pregnancy test, if applicable)	X[4]								
C-SSRS	X								
Distribute study drug kits	X								
Review inhaler training	X								
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion	X[5]								
UPDRS Part 3		X[6]		X	X	X	X		
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule next visit								X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)								X	
Post-TV5 telephone contact: call patient 2 weeks (± 3 days) before TV6									X

[1]Dosing of study medication occurs at least 1 hour after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Assessment can be done at any point after arrival, but must be completed before dosing.
[4]Document whether patient is fasting (≥4 hours after last snack or meal).
[5]The PD Diary is to be completed for the 3 consecutive days prior to TV6; the Inhaled Dosing Log is to be completed daily through TV6.
[6]Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

APPENDIX 13: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 5 (OV5) (9 MONTHS [36±2 WEEKS] AFTER OV1)

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV5	Post- OV5 Telephone Contact
Confirm DLco assessment[1] has been performed prior to visit; and if not complete, re-schedule study visit	X		X
Record any changes in usual PD medication dose/regimen	X		
Record any changes in concomitant medications	X		
Physical examination (brief)	X		
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X		
Spirometry (preferably in ON state)	X (ON)		
Clinical laboratory tests (serum pregnancy test, if applicable)	X[2]		
C-SSRS	X		
Monitor for AEs	X		
Schedule next visit		X	
Schedule DLco visit at pulmonary site (14±3 days before next visit)		X	
Post- OV5 telephone contact: call patient 2 weeks (± 3 days) before OV6			X

[1]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[2]Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 14: TIME AND EVENTS TABLE—TREATMENT VISIT 6 (TV6) (12 MONTHS [52±2 WEEKS] AFTER TV1)/EARLY WITHDRAWAL VISIT

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV6	Post-TV6 Assessments
Collect, review, sign, and date PD Diary and Inhaled Dosing Log	X								
Collect empty capsules, inhalers, and unused supplies	X								
Confirm DLco assessment[2] has been completed prior to visit; if not done, the study visit must be re-scheduled[3]	X								
Record any changes in usual PD medication dose/regimen	X								
Record time of patient's prior usual PD medication dose	X								
Record any changes in concomitant medications	X								
PDQ-39 (preferably in ON state)	X[4]								
PGI-C (preferably in ON state)	X[4]								
UPDRS Part 2 (preferably in ON state)	X[4]								
S&E ADL (preferably in ON state)	X[4]								
UPDRS Part 4 (Questions 32-35 and 36-39)	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR and RR and orthostatic BP and HR)	X[5]								
Electrocardiogram	X								
C-SSRS	X								
Epworth Sleepiness Scale	X								
QUIP	X								
Spirometry (preferably in ON state)	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[6]								
Provide new inhaler for treatment		X							
UPDRS Part 3		X[7]		X	X	X	X		
Self-administration of study drug (in OFF state)			X[1]						

Procedures	Arrival	Pre-dose	Time 0 (Dosing)[1]	10 min Post-dose	20 min Post-dose	30 min Post-dose	60 min Post-dose	End of TV6	Post-TV6 Assessments
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule DLco visit[2] to occur at pulmonary site in 4-5 weeks								X	
Post-TV6 DLco assessment[2] at 4-5 weeks after TV6 or Early Withdrawal Visit[3]									X

[1]Dosing of study medication occurs at least 1 hour after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[2]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[3]Patients who withdraw early will undergo all of the TV6 assessments except the pre-TV6 DLco assessment. Patients will be scheduled to undergo the post-TV6 DLco assessment 4-5 weeks after completion of the Early Withdrawal Visit.
[4]Preferably in the ON state, but these must be performed before any other study evaluation.
[5]Assessment can be done at any point after arrival but must be completed before dosing.
[6]Document whether patient is fasting (≥4 hours after last snack or meal).
[7]Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

APPENDIX 15: TIME AND EVENTS TABLE—OBSERVATIONAL VISIT 6 (OV6) VISIT (12 MONTHS [52±2 WEEKS] AFTER OV1)/EARLY WITHDRAWAL VISIT

Procedures	Assess in Either ON or OFF State Unless Otherwise Noted	End of OV6	Post- OV6 Assessments
Confirm DLco assessment[1] has been performed prior to visit; and if not complete, re-schedule study visit[2]	X		
Record any changes in usual PD medication dose/regimen	X		
Record any changes in concomitant medications	X		
PDQ-39 (preferably in ON state)	X (ON)[3]		
UPDRS Part 2 (preferably in ON state)	X (ON)[3]		
S&E ADL (preferably in ON state)	X (ON)[3]		
Physical examination (brief)	X		
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X		
Electrocardiogram	X		
Spirometry (preferably in ON state)	X (ON)		
C-SSRS	X		
Epworth Sleepiness Scale	X		
QUIP	X		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[3]		
Monitor for AEs	X		
Schedule DLco visit[1] to occur at pulmonary site in 4-5 weeks		X	
Post- OV6 DLco assessment[1] at 4-5 weeks after OV6 or Early Withdrawal Visit[2]			X

[1]DLco is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry. Preferably in the ON state.
[2] Patients who withdraw early will undergo all of the OV6 assessments except the pre- OV6 DLco assessment. Patients will be scheduled to undergo the post- OV6 DLco assessment 4-5 weeks after completion of the Early Withdrawal Visit.
[3]Preferably in the ON state, but these must be performed before any other study evaluation.
[4]Document whether patient is fasting (≥4 hours after last snack or meal).

APPENDIX 16: IN-CLINIC ASSESSMENT OF ON/OFF STATES AND DYSKINESIA

An "OFF state" is defined as the time when medication has worn off and is no longer providing benefit with respect to mobility, slowness, and stiffness. OFF episodes may be heralded by non-motor symptoms (e.g., pain, anxiety) prior to the appearance of motor symptoms.

An "ON state" is defined as the time when medication is providing benefit with respect to mobility, slowness, and stiffness, and may or may not be providing complete alleviation of all PD symptoms.

For recording motor state in the PD Diary, when patients are in an ON state, the presence and extent of dyskinesia (involuntary twisting, turning movements that are an effect of medication) will also be noted:

- ON with no dyskinesia
- ON with non-troublesome dyskinesia (ON with dyskinesia that does not interfere with function or cause meaningful discomfort)
- ON with troublesome dyskinesia (ON with dyskinesia that interferes with function or causes meaningful discomfort)

These ON and OFF definitions are to be used in training the patients to recognize and record their ON and OFF states. Patients will record their ON and OFF states in their diaries at home.

In the clinic, the examiner will note the occurrence of dyskinesia during the 60-minute post-dose period and the maximum severity (mild, moderate, or severe) of any dyskinesia during the 60-minute post-dose period. The examiner will also note if the patient converts to the ON state during the 60-minute post-dose period and if so, whether the patient is still in the ON state at 60 minutes post-dose.

APPENDIX 17: LABORATORY PARAMETERS

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

Urea	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein

Other screening tests

Pregnancy test (serum) at screening (SV1 or SV2) and at TV/OV1, TV/OV3, TV/OV4, TV/OV5, and TV/OV6, if applicable; magnesium; C-Reactive Protein

APPENDIX 18: UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communication hydrocephalus on imaging study
- Negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3. Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with Step 1:

- Unilateral onset
- Rest tremor present
- Progressive disorder

- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

*From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.

APPENDIX 19: MODIFIED HOEHN AND YAHR PD SEVERITY SCALE ASSESSMENT

The modified Hoehn and Yahr PD severity assessment uses the following scale:

- Stage 0 = No signs of disease.
- Stage 1 = Unilateral disease.
- Stage 1.5 = Unilateral plus axial involvement.
- Stage 2 = Bilateral disease, without impairment of balance.
- Stage 2.5 = Mild bilateral disease, with recovery on pull test.
- Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
- Stage 4 = Severe disability; still able to walk or stand unassisted.
- Stage 5 = Wheelchair-bound or bedridden unless aided.

APPENDIX 20: CONTRAINDICATIONS TO PERFORMING ROUTINE SPIROMETRY

- Recent myocardial infarction or unstable angina within 1 month
- Hemoptysis
- Pneumothorax, current or within prior 3 months
- Pulmonary embolus within prior 3 months
- Thoracic, abdominal, or cerebral aneurysms
- Recent eye surgery within prior 3 months
- Presence of an acute disease process that might interfere with test performance
- Recent surgery of thorax or abdomen
- Any history of syncope associated with forced exhalation

APPENDIX 21: CVT-301 SYSTEM ADDITIONAL INFORMATION

All instructions for how to properly use the CVT-301 system are outlined in the Instructions for Use document that is included with every CVT-301 study kit. The following additional observations by patients when using the system have been noted by some investigational sites:

- Patients may experience black sputum. No clinical correlate to this finding occurred (small number of patients)
- Patients may see powder emitted from the inhaler while completing an inhalation.
- Patients may see powder emitted from their mouths when exhaling after use of the system.
- Patients may note some built-up powder falling off of the inhaler following multiple uses. Although cleaning is not necessary, system cleaning instructions are noted under the "More Information" section of the Instructions for Use.
- Patients may attempt to push the capsule through the foil instead of peeling the blister open which can damage the capsule and impair drug delivery. Make sure patients are informed not to push the capsule through the foil.
- Patients may not hear the "whirl" of the capsule upon inhalation. As noted in the Instructions for Use, if this occurs patients should repeat the inhalation steps to ensure that the drug is delivered. If whirling sound is still not heard, patients should:
    - Check that a capsule is inserted
    - Make sure mouthpiece is firmly attached
    - Inhale deeper or longer