CLINICAL STUDY PROTOCOL

Protocol Title:	A 14-Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations OFF Phenomena)
Protocol Number:	CVT-301-004E
US IND Number:	115750
EudraCT Number:	2015-005626-19
Development Phase:	Phase 3
Study Sponsor:	Civitas Therapeutics, Inc. 190 Everett Ave Chelsea, MA 02150 USA
Protocol Version:	5.2
Version Date:	07-Dec-2016

CIVITAS THERAPEUTICS PROTOCOL APPROVAL PAGE

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:	[redacted]
Sponsor's Responsible Medical Director:	[redacted]
CRO Global Study Manager:	[redacted]
CRO Medical Monitor:	[redacted]
CRO Safety (Pharmacovigilance) Reporting:	[redacted]
Clinical Laboratory:	[redacted]
Spirometry and ECG Central Laboratory	[redacted]

DLco-Related Services and Analysis	[redacted]
Rater Training, Diary, and Endpoint Surveillance	[redacted]

2. SYNOPSIS

Title of Study:	A 14-Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena)
Protocol Number:	CVT-301-004E
Investigators/Study Sites:	This study will be conducted at approximately 70 sites in the United States of America (USA), Canada, and Europe.
Phase of Development:	3
Objectives:	**Primary Objective** • To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/ FVC ratio) over a 14-month period. **Secondary Objectives** • 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 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 Schwab and England (S&E) Activities of Daily Living (ADL) score. • Change from baseline visit 9-Item Patient Health Questionnaire (PHQ-9). • Change from baseline visit Impact of Parkinson's OFF Episodes Patient Survey • Change from baseline visit UPDRS Part 2 score. **Safety Objectives** • To characterize the effects of CVT-301 on safety over a 14-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, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Amphetamine Withdrawal Questionnaire (AWQ), the Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS) . • To describe the effects of CVT-301 on DLco. • To compare the pulmonary safety, as assessed by spirometry (FEV1 and FEV1/FVC ratio) between the group of patients who were treated with CVT-301 in study CVT-301-004 versus the patients treated with placebo in CVT-301-004. • Change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Questions 32-35] and wearing off [Questions 36-39]). • Occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic.
Study Design:	This study is a 14-month, dose-level blinded, multicenter study of 2 inhaled dose levels of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes). The 14 month period includes a 4-week drug holiday to administer withdrawal assessments. All patients will receive active treatment, but patients will be blinded to dose level. This will serve as an extension to the CVT-301-004 study for those patients who participated in that study and remain eligible for this study. In addition, patients who completed study CVT-301-009 per protocol may be enrolled if they meet the CVT-301-004E eligibility criteria. Patients who are CVT-301-naïve, including patients who were randomized to the observational arm of the CVT-301-005 study, also may be enrolled if they meet the CVT-301-004E eligibility criteria. Patients must have completed all of the preceding CVT-301 study visits per protocol without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from the CVT-301-004, CVT-301-009 or CVT-301-005 studies prior to completion, *for any reason*, will not be eligible. Patients who are already enrolled in CVT-301-004E under the prior version of this protocol, including any former CVT-301-003 study patients, will be re-consented to continue in the study under the current amendment. No new patients from the CVT-301-003 study will be permitted to enter the CVT-301-004E study. New patients from CVT-301-004, patients from CVT-301-009, patients from the observational arm of CVT-301-005, and other new CVT-301 naïve patients who meet eligibility criteria will be enrolled in CVT-301-004E under the current amendment. Patients who received CVT-301 in the double-blinded CVT-301-004 study will remain on their same blinded dose level: patients who

	received DL1 (target nominal dose of 35 mg levodopa [LD] fine particle dose [FPD]) in CVT-301-004 will receive DL1 (target nominal dose of 35 mg LD FPD) in CVT-301-004E. Patients who received DL2 (target nominal dose of 50 mg LD FPD) in CVT-301-004 will receive DL2 (target nominal dose of 50 mg LD FPD) in CVT-301-004E. Patients who received placebo in CVT-301-004, and all former CVT-301-009 patients, as well as any additional CVT-301-naïve patients, will be randomized in 1:1 ratio to DL1 or DL2 in the CVT-301-004E study. Randomization will be differentiated by the patient's Hoehn and Yahr disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity 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%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used. Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode) to deliver the intended dose. Capsules for DL1 and DL2 will appear identical in order to maintain blinding. The study includes a screening period of up to 35 days (for CVT-301-naïve patients and patients from the CVT-301-009 study) and a treatment period of approximately 13 months. The screening visits are not required for CVT-301-004 patients. CVT-301-004 patients will have a 1- to 14-day period between the last dose of study drug in the CVT-301-004 study and the first dose of study drug in this study. A longer period may be permitted with approval from the Sponsor. Planned visits will occur at 0, and approximately 1, 3, 6, 9, and 14 months. For CVT-301-naïve patients and CVT-301-009 patients, spirometry will be assessed at the neurology sites for screening and TV1. The baseline DLco will be performed at dedicated pulmonary sites prior to TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry and DLco after TV1 (within 2 weeks prior to the 3-, 6-, 9-, and 14-month visits, and 4 to 5 weeks following completion of Treatment Visit 6 [TV6]). For patients from CVT-301-004, spirometry will be assessed at the neurology sites at TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry and DLco after TV1 as described for the CVT-301-naïve patients. For all patients, the treatment period will be approximately 13 months (56±2 weeks) in duration. The maximum anticipated duration of this study for patients from the CVT-301-004 study will be approximately 67 weeks, including the final spirometry and DLco assessment which takes place 4 to 5 weeks following the treatment period. The maximum anticipated duration of this study for CVT-301-naïve patients and CVT-301-009 patients, including the screening period and the final spirometry and DLco assessments, will be approximately 72 weeks. 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 the 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.). If a patient has a dose reduction due to tolerability concerns, he/she may be titrated back up to his/her randomized dose (i.e., 2 capsules) at the next scheduled study visit if the investigator determines that the tolerability issue has adequately resolved and the patient could potentially benefit from escalating back up to the original randomized dose level (i.e., 2 capsules). This return to randomized dose may take place at the in-clinic visit or in between visits (if the patient and clinic staff talk by telephone) and may only be done once during the study. Clinic staff will call the patient 1-2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has a tolerability-related dose reduction is re-escalated to the randomized dose and experiences another tolerability issue related to dose level that requires dose reduction, he/she will be dose reduced for a second time and will remain on that dose for the remainder of the study; he/she will not be eligible for any additional up-titration to the original dose. All patients should continue with their usual prescribed standard PD medication regimen for the study duration. This regimen may be altered if needed during the course of the 14-month study. The addition or modification of medications or treatments may include other forms of oral medications **except** oral "as needed" (PRN) PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study.** Safety data will be reviewed by an independent Data Safety Monitoring Board (DSMB) that will include relevant experts as defined in the DSMB Charter. There will be no prospective interim evaluation of efficacy endpoint data. **Screening Period** CVT-301-naïve patients (including CVT-301-005 observational arm patients) and patients from the CVT-301-009 study will undergo a screening period (of up to 35 days) prior to randomization. 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). CVT-301-004 patients will not be required

	to undergo the screening visits and will undergo TV1 after a 1- to 14-day period (or longer if approved by the Sponsor) following Treatment Visit 4 (TV4) of the CVT-301-004 study. **SV1 for CVT-301-Naïve Patients and CVT-301-009 Patients Within 35 days prior to randomization** 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), concurrent conditions, and PD history will be documented. PD diagnosis will be confirmed in the ON state using Steps 1 and 2 of the United Kingdom (UK) Brain Bank Criteria and PD severity will be staged using 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 the 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 Parts 1, 2, 3 and 4 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 dyskinesias. 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 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 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 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). **SV2 for CVT-301-Naïve Patients and CVT-301-009 Patients 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/regimen. Any changes in concomitant medication 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 also 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. 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), UPDRS Parts 1, 2 and 4 (assessed in the ON state), ON/OFF concordance testing (assessed in both ON and OFF states), and clinical laboratory tests (with documentation of fasting status) including serum pregnancy tests, if applicable. In addition the following assessments will be recorded, preferably in the ON state: the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP); the Epworth Sleepiness Scale; and the Columbia-Suicide Severity Rating Scale (C-SSRS). 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. During the 3 consecutive days prior to TV1, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for TV1, the patients will take all of their usual prescribed non-PD medications and PD medications, including LD-containing PD medications. Following completion of SV2 and prior to randomization (for CVT-301-naïve patients and CVT-301-009 patients), eligibility criteria will be reviewed by delegated staff. Before TV1, patients will be assigned/randomized to treatment. Patients who received DL1 (target nominal dose of 35 mg LD FPD) in the CVT-301-004 study will receive DL1 (target nominal dose of 35 mg LD FPD) in this study, and patients who received DL2 (target nominal dose of 50 mg LD FPD) in the CVT-301-004 study will receive DL2 (target nominal dose of 50 mg LD FPD) in this study. Patients who received placebo in the CVT-301-004 study, CVT-301-009 patients and CVT-301-naïve patients will be randomized in a 1:1 ratio to DL1 or DL2. If a patient meets final eligibility requirements, eligibility will be reviewed by delegated staff. Randomization will

	be differentiated by the patient's Hoehn and Yahr disease severity rating (<2.5 versus ≥2.5) to balance for disease severity 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%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used. Patients and site staff will be blinded to treatment level. The clinic staff will schedule the next visit and schedule patients to undergo DLco assessment at the pulmonary function lab. This should be scheduled to occur after SV2 and before TV1, and should be performed with the patient in the ON state (as reported by the patient to the pulmonary technician). As part of the visit, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry. Clinic staff will arrange to speak with patients by telephone approximately 4-6 days prior to TV1 confirm the DLco assessment has been done or is scheduled to occur prior to TV1, to confirm the next study visit, and to remind patients of the study procedures required prior to the next scheduled study visit (including the DLco assessment and 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 TV1 and that they should contact the site if an intervening illness occurs prior to TV1. 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 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. **Treatment Period** The assessments and procedures performed at TV1 will differ for patients entering from the CVT-301-004 study and for CVT-301-naïve patients and prior CVT-301-009 patients. **CVT-301-004E TV1 for patients entering from CVT-301-004 1 to 14 days after TV4 in the CVT-301-004 Study** Informed consent will be obtained prior to receiving drug for this extension study. Patients should provide written informed consent for this study at TV4 of the CVT-301-004 study. Patients will be instructed to take their prescribed oral PD medications on their usual schedule. The timing of arrival for TV1 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 of their usual PD

	medications. The following assessments will be performed: recording of usual PD medications; recording of time of usual PD medication taken prior to the visit; recording of concomitant medication; full physical examination; 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; the C-SSRS assessment, Epworth Sleepiness Scale, and UPDRS Parts 1 and 2 (preferably in the ON state). In addition, the following assessments will be recorded: the Patient Health Questionnaire-9 (PHQ-9), AWQ, and DDS-PC (all in the ON state) and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). Patients will be trained again on the proper technique to prepare and use the inhaler system (using sham capsules) per the IFU. The clinic staff will distribute 2 outpatient data collection tools: (1) *PD Diary*: 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 Treatment Visit 2 [TV2], Treatment Visit 3 [TV3], TV4, Treatment Visit 5 [TV5], and TV6). (2) *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 13-month treatment period). The clinic staff will distribute the study drug kits. Under clinic staff supervision, preferably between 2 and 5 hours after receiving their previous dose of PD medications (in the OFF state), patients will prepare and self-administer study their entire dose of inhaled study drug. Spirometry evaluations will be performed immediately prior to inhalation, and at 15, 30, and 60 minutes post-dose. At the time of each spirometry assessment, staff will record the patient's motor state. If within the first 60 minutes after inhalation, the patient's spirometry assessment shows <u>either</u> of the following, the patient will NOT be sent home with study drug, and the site will follow the Spirometry Alert and Review Process: a decrease in FEV1 $\geq$ 20% <u>AND</u> a decrease in FEV1 by 200 mL compared with pre-dose results, <u>and/or</u> a reduction in the FEV1/FVC ratio to <60%. If either criteria are met, the patient will NOT be sent home with study drug and the following procedures will be followed: (1) manage any emergent medical conditions, if necessary; (2a) complete a Spirometry Alert and Review Worksheet, including documentation of medical assessments and recording the presence/absence of pulmonary and any other signs or symptoms, and transmit the worksheet to prespecified personnel; (2b) immediately transmit the spirometry assessments to the Spirometry Core Laboratory; and (3) complete all other TV1 safety assessments.

	The site will ensure that the patient is clinically stable before leaving the site. Spirometry assessments will be over-read by the Spirometry Core Laboratory. If abnormal ranges in spirometry values are determined likely to be related to problems in spirometry/breathing technique and/or related to disordered neuromuscular strength or coordination as is frequently observed with PD patients, the patient will be permitted to repeat the visit. The medical monitor and Sponsor will determine whether or not the patient may continue study participation (when possible, this determination will be completed within 48 hours). If the patient is cleared to continue study participation, TV1 will be repeated in its entirety. If upon repeated testing abnormal spirometry results are seen again, the same procedures will be followed; the patient may still be eligible for participation, after consultation with the medical monitor, if it is documented that the abnormal results are not related to pulmonary disease. Vital signs (standard and orthostatic 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). Patients will remain in the clinic until completion of the safety evaluations. The next visit will be scheduled. 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. Additionally, clinic staff will arrange to speak with patients by telephone 1 week before TV2 to monitor for AEs, to discuss concerns or challenges with the inhaler systems or Inhaled Dosing Log, to confirm the next visit, to ask the patients how many empty study drug kits will be returned at the next visit, and to remind patients to complete the PD Diary and Inhaled Dosing Log. **TV1 for CVT-301-Naïve Patients and CVT-301-009 Patients** **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 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 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 of their usual PD medications. The clinic staff will collect the Screening ON/OFF Episodes Log and PD Diary and review the information, sign and date each, and will

	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 the standard PD medication dose/regimen. The following assessments will be performed: review of concomitant medication; a brief physical examination, standard and orthostatic vital sign assessments (BP, HR, and RR), and ECG. In addition, the following assessments will be recorded: PDQ-39, the Patient Health Questionnaire-9 (PHQ-9), AWQ, DDS-PC, all assessed in the ON state; UPDRS Part 1 and Part 2 (preferably in ON state); S&E ADL scale (preferably in ON state); UPDRS Part 4 (Questions 32-35 and 36-39); QUIP; Epworth Sleepiness Scale; C-SSRS; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). Patients will also undergo spirometry (preferably in ON state), and clinical laboratory tests (with documentation of fasting status) including serum pregnancy test, if applicable. Patients will be trained again on the proper technique to prepare and use the inhaler system (using sham capsules) per the IFU. The clinic staff will distribute 2 outpatient data collection tools: (1) *PD Diary*: 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 TV6). (2) *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 13-month treatment period). The clinic staff will provide study drug kits. 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 previous dose of PD medications (in the OFF state), patients will prepare and self-administer study their entire dose of inhaled study drug. Spirometry evaluations will be performed immediately prior to inhalation, and at 15, 30, and 60 minutes post-dose. At the time of each spirometry assessment, staff will record the patient's motor state. If within the first 60 minutes after inhalation, the patient's spirometry assessment shows <u>either</u> of the following, the patient will NOT be sent home with study drug, and the site will follow the Spirometry Alert and Review Process: a decrease in FEV1 $\geq$ 20% <u>AND</u> a decrease in FEV1 by 200 mL compared with pre-dose results, <u>and/or</u> a reduction in the FEV1/FVC ratio to <60%. If either criteria are met, the patient will NOT be sent home with study drug and the following procedures will be followed: (1) manage any emergent medical conditions, if necessary; (2a)

	complete a Spirometry Alert and Review Worksheet, including documentation of medical assessments and recording the presence/absence of pulmonary and any other signs or symptoms, and transmit the worksheet to prespecified personnel; (2b) immediately transmit the spirometry assessments to the Spirometry Core Laboratory; and (3) complete all other TV1 safety assessments. The site will ensure that the patient is clinically stable before leaving the site. Spirometry assessments will be over-read by the Spirometry Core Laboratory. If abnormal ranges in spirometry values are determined likely to be related to problems in spirometry/breathing technique and/or related to disordered neuromuscular strength or coordination as is frequently observed with PD patients, the patient will be permitted to repeat the visit. The medical monitor and Sponsor will determine whether or not the patient may continue study participation (when possible, this determination will be completed within 48 hours). If the patient is cleared to continue study participation, TV1 will be repeated in its entirety. If upon repeated testing abnormal spirometry results are seen again, the same procedures will be followed; the patient may still be eligible for participation, after consultation with the medical monitor, if it is documented that the abnormal results are not related to pulmonary disease. Vital signs (standard and orthostatic 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). The next visit will be scheduled. 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. Additionally, clinic staff will arrange to speak with patients by telephone 1 week before TV2 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, 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, 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). **<u>At-Home Dosing for all Patients</u>** At TV1, TV2, TV3, TV4, and TV5, patients will receive study drug kits and the IFU to take home with them, except during the study drug holiday. Patients will also receive study drug kits and the IFU to take home with them at TV4.1, TV5.1, or at an Unscheduled Visit. Patients will be instructed to continue with their usual prescribed standard PD medication regimen for the study duration.

	This regimen may be altered if needed during the course of the 14-month study. The addition or modification of medications or treatments may include other forms of oral medications **except** oral PRN PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study**. Any modifications to the standard PD dose and/or regimen will be recorded in the electronic case report form (eCRF). 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. Patients may not take oral PRN medications to manage OFF states during the study. *Note: If Study CVT-301-009 supports the safety and tolerability of CVT-301 administration in the early morning, investigators will be informed that participants in the current study CVT-301-004E can start to take study drug for early morning OFF periods. Until that time study drug may **not** be used to treat morning akinesia. 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 oral 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 13-month treatment period. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV1 and 1 week prior to each visit for TV2, TV3, TV4, TV5, and TV6.

	Patients will bring the PD Diary, Inhaled Dosing Log, empty capsules, inhalers, and unused supplies to the clinic visit. **TV2 for all Patients** **1 month (4 weeks ±5 days) after TV1** Patients will complete the PD Diary for the 3 consecutive days prior to TV2, and patients will complete 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). Clinic staff will collect, review, sign and date all PD Diary and Inhaled Dosing Log and will collect empty capsules, inhalers, and unused supplies. Clinic staff will record any changes in the standard PD medication dose/regimen and will 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 medication; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); and ECG. In addition the following assessments will be recorded: PDQ-39, PHQ-9 and PGI-C (all assessed in an ON state); UPDRS Part 2 (preferably in the ON state); S&E ADL scale (preferably in the ON state); UPDRS Part 4 (Questions 32-35 and 36-39); QUIP; Epworth Sleepiness Scale; C-SSRS; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). The clinic staff will provide study drug kits and review the inhaler training. The staff will also 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 prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) the occurrence and severity of dyskinesia and (2) 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). Clinic staff will also schedule a DLco and spirometry assessment to occur at the pulmonary function facility within 2 weeks prior to the next visit. These assessments should be performed in an ON state (as reported by the patient to the pulmonary technician). As part of the visit, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry. The next study visit will be scheduled. Clinic staff will arrange to speak with patients by phone 1 week prior to TV3 to address any potential concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm that the DLco and spirometry visit at the pulmonary function lab has taken place or has been 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 Inhaled Dosing Log). **TV3 for all Patients** **3 months (12±2 weeks) after TV1** Patients will complete the PD Diary for the 3 consecutive days prior to TV3, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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). Clinic staff will collect, review, sign, and date the PD Diary and Inhaled Dosing Log and will collect empty capsules, inhalers, and unused supplies. They will confirm that the DLco and spirometry visit has taken place within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in the standard PD medication dose/regimen and will 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 medication; a brief physical examination, standard

	and orthostatic vital sign assessments (BP, HR, and RR), ECG; 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 and PHQ-39, both assessed in the ON state, PGI-C scale, UPDRS Part 2 and S&E ADL (each preferably assessed in the ON state prior to other study evaluations); UPDRS Part 4 (Questions 32-35 and 36-39); C-SSRS; Epworth Sleepiness Scale; QUIP; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). The clinic staff will provide study drug kits and review the inhaler training (if needed). The staff will also provide the PD Diary and Inhaled Dosing Log and review instructions for completion. The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) the occurrence and severity of dyskinesia, and (2) 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). Clinic staff will also schedule a DLco and spirometry assessment to occur at the pulmonary function facility within 2 weeks prior to the next visit. These assessments should be performed in an ON state (as reported by the patient to the pulmonary technician). As part of the visit, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry. The next study visit will be scheduled. Clinic staff will arrange to speak with patients by phone 1 week prior to TV4 to address any potential concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm that the DLco and spirometry visit at the pulmonary function lab has taken place or has been 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 Inhaled Dosing Log). **TV4 for all Patients** **6 months (24±2 weeks) after TV1** Patients will complete the PD Diary for the 3 consecutive days prior to TV4, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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). Clinic staff will collect, review, sign, and date the PD Diary and Inhaled Dosing Log and will collect empty capsules, inhalers, and unused supplies. They will confirm that the DLco and spirometry visit has taken place within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in the standard PD medication dose/regimen and will 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 medication; full physical examination; standard vital signs (BP, HR, and RR and orthostatic vital signs (BP and HR); ECG; 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 and PHQ-9, both assessed in the ON state; PGI-C scale, UPDRS Part 2 and S&E ADL (each preferably assessed in the ON state prior to other study evaluations); UPDRS Part 4 (Questions 32-35 and 36-39); C-SSRS; Epworth Sleepiness Scale; QUIP; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). The clinic staff will provide study drug kits and review the inhaler training (if needed) for patients not entering the study drug holiday. The staff will also provide the PD Diary and Inhaled Dosing Log and review instructions for completion. The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) the occurrence and severity of dyskinesia, and (2) 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). The next study visit will be scheduled. Clinic staff will arrange to speak with patients by phone 1 week prior to TV5 to address any potential concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, 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 Inhaled Dosing Log). 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 maneuver will be performed, followed by DLco, and then spirometry. **TV5 for all Patients** **9 months (36±2 weeks) after TV1** Patients will complete the PD Diary for the 3 consecutive days prior to TV5, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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). Clinic staff will collect, review, sign, and date the PD Diary and Inhaled Dosing Log and will collect empty capsules, inhalers, and unused supplies. They will confirm that the DLco and spirometry visit has taken place within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in the standard PD medication dose/regimen and will 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 medication; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; 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, PHQ-9, and PGI-C scale (all assessed in the ON state), UPDRS Part 2 and S&E ADL (each preferably assessed in the ON state prior

	to other study evaluations); UPDRS Part 4 (Questions 32-35 and 36-39); C-SSRS; Epworth Sleepiness Scale; QUIP; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). The clinic staff will provide study drug kits and review the inhaler training (if needed) for patients not entering the study drug holiday. The staff will also provide the PD Diary and Inhaled Dosing Log and review instructions for completion. The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) the occurrence and severity of dyskinesia, and (2) 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). Clinic staff will also schedule a DLco and spirometry assessment to occur at the pulmonary function facility within 2 weeks prior to the next visit. These assessments should be performed in an ON state (as reported by the patient to the pulmonary technician). As part of the visit, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry. The next study visit will be scheduled.* Clinic staff will arrange to speak with patients by phone 1 week prior to TV6 to address any potential concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm that the DLco and spirometry visit at the pulmonary function lab has taken place or has been done, 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 Inhaled Dosing Log). *Patients who have already completed TV5 at the time of implementation of protocol Version 5.2 will have the option to consent to this amendment at an Unscheduled Visit prior to TV6, at which time they will receive an additional 4 weeks of study drug so that TV6 can be scheduled for approximately 13 months (56±2 weeks) after TV1. These patients will participate in the withdrawal sub-study post-TV6 as described below. **TV6 for all Patients/ Early Withdrawal Visit** **13 months (56±2 weeks) or 14 months (60 ±2 weeks) after TV1** Treatment Visit 6 will constitute the end-of-study visit. Patients will

	complete the PD Diary for the 3 consecutive days prior to TV6, and patients will complete the Inhaled Dosing Log daily up until TV6. They 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). Clinic staff will collect, review, sign, and date the PD Diary and Inhaled Dosing Log and will collect empty capsules, inhalers, and unused supplies. They will confirm that DLco and spirometry visit at the pulmonary function lab was performed within 2 weeks prior to the visit (and if not, re-schedule the study visit). Clinic staff will record any changes in the standard PD medication dose/regimen has not changed and will 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 medication; brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; 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, PHQ-9, and PGI-C scale (all assessed in the ON state), UPDRS Part 2 and S&E ADL (each preferably assessed in the ON state prior to other study evaluations); UPDRS Part 4 (Questions 32-35 and 36-39); C-SSRS; Epworth Sleepiness Scale; QUIP; and the Impact of Parkinson's OFF Episodes Patient Survey (preferably in the ON state). The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug. The dosing time is preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) 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. Once all of the assessments are complete, schedule the patient to undergo a DLco and spirometry assessment 4 to 5 weeks after completion of TV6. These assessments 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. **Sub-Study to Assess Potential Withdrawal Symptoms** After patients are consented to protocol Version 5.2, they will participate in a withdrawal symptom sub-study at the end of TV4, TV5, or TV6, depending on which of the visits is the next scheduled one for the patient. In addition to the assessments detailed in the sections above for the treatment visit, the AWQ and DDS-PC will be performed upon arrival in the ON state, and the UPDRS Part 1 will be performed preferably in the ON state. When study activities for the visit are completed, patients will begin a 28-day period of assessment of potential drug withdrawal symptoms. To this end, patients who are at TV4 or TV5 at the time of consent will go on a study drug holiday for this time period. All patients in the withdrawal sub-study (patients consented to protocol Version 5.2) will be given copies of the AWQ, the DDS-PC, PHQ-9, Epworth Sleepiness Scale, C-SSRS (self-report version), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS) to be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after the treatment visit. Patients should fill out the questionnaires during their first ON state (after the intake of their first scheduled dose of standard oral PD medication) on each of these days. The site will call patients at 14 (±3) days after the treatment visit to remind them to complete the questionnaires, and to inquire about potential adverse events and changes in concomitant medications. Patients who enter the withdrawal sub-study after TV6 will also receive a call at 28 (±3) days. Patients who entered the study drug holiday will be scheduled to return to the clinic for a drug re-supply visit and resumption of the full course of study treatment. Patients who entered the withdrawal sub-study after TV6 will be completed with the study after they return the questionnaires and undergo the DLco and spirometry assessment 4 to 5 weeks after completion of TV6, as described in the TV6 section. Patients who withdraw prematurely will complete the TV6 assessments (not including the pre-TV6 DLco and spirometry assessment) at the time of withdrawal and will be scheduled to undergo a DLco and spirometry assessment 4 to 5 weeks after completion of the Early Withdrawal Visit. Patients who withdraw prematurely and prior to participating in the sub-study to assess potential withdrawal symptoms will complete the withdrawal assessments during the 28 days following completion of the TV6 assessments.
Selection of Patients:	CVT-301-004, CVT-301-005 observational arm, and CVT-301-009 study patients who have met the eligibility criteria for CVT-301-004E and who have completed all prior study visits per protocol without any safety issues that would preclude participation in this study according to the investigator are eligible for participation in

	this study. Patients who withdrew from any of the prior studies prior to completion, *for any reason*, will not be eligible. Other CVT-301-naïve patients must meet all of the inclusion criteria and must not meet any of the exclusion criteria. **Inclusion Criteria (not assessed for the CVT-301-004 study patients):** • 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 86 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 United Kingdom (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 • 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 (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 patients with an FEV1 that is ≥ 50% to < 60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine eligibility. 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 cell transplantation) or plan to have stereotactic surgery during the study period. Patients who have had deep brain stimulation [DBS] will also be excluded unless the procedure was performed more than 6 months prior to study enrollment. • Patients with a history of psychotic symptoms requiring treatment, or suicidal ideation or attempt within the prior 12 months. • 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 16 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 unable to comply with study procedures or make them unsuitable for their participation in the study. • Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety. Potential issues of concern should be raised to the medical monitor during eligibility review. • For new CVT-301 naïve patients, 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).
Planned Sample Size:	The study is planned is to enroll approximately 390 patients to ensure that approximately 290 patients will complete the 12 month study. All patients who completed the CVT-301-004 and the CVT-301-009 study per protocol without any safety issues are eligible. In addition, CVT-301-naïve patients, including those who participated in the CVT-301-005 observational arm may be enrolled to achieve the planned enrollment.
Investigational Therapy:	**CVT-301 (levodopa inhalation powder [LIP])** Two CVT-301 dose levels will be investigated. Each dose level 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 for patients randomized to DL1 (target nominal respirable dose of approximately 35 mg LD FPD) will deliver approximately 17.5 mg LD FPD to the lung per capsule inhalation. The capsules provided for patients randomized to DL2 (target nominal respirable dose of approximately 50 mg LD FPD) will deliver approximately 25 mg LD FPD to the lung per capsule inhalation. In order to maintain the blind to treatment assignment, all patients will be given identical-looking study drug kits and instructed to inhale 2 capsules sequentially for each dose (1 capsule for each inhalation) for each dose. Patients may sip water in between capsule inhalations, if needed.
Reference Therapy:	None.
Treatment Duration:	The planned treatment period will be 52 ±2 weeks for all patients. Each patient will self-administer up to 5 doses of inhaled study drug per day. The maximum anticipated study duration for patients from the CVT-301-004 study will be approximately 59 weeks, including

	the final DLco assessment which takes place 4 to 5 weeks following the treatment period. The maximum anticipated duration of this study for CVT-301-naïve patients and CVT-301-009 patients, including the screening period and the final DLco assessment, will be approximately 64 weeks.
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 be also assessed from physical examinations, AE reporting, standard and orthostatic vital signs (BP, RR, and HR), clinical laboratory values (hematology and biochemistry), ECGs, the QUIP, Epworth Sleepiness Scale, the C-SSRS, the AWQ, the DDS-PC, and the self-administered MDS-UPDRS Parts 1B and 2. Additionally, safety will be assessed with: • Occurrence and severity of examiner-rated dyskinesia after study drug is administered in the clinic. • UPDRS Part 4 (Questions 32-35 and 36-39) **Efficacy** • 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 • PHQ-9 • Impact of Parkinson's OFF Episodes Patient Survey • PGI-C • S&E ADL • UPDRS Part 2 Based on Out-Patient Evaluations: • 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.
Statistical Methods and Planned Analyses:	For all statistical analyses, the visit at which the CVT-301 treatment is initiated will be used as the baseline. This will be TV1 from the CVT-301-004 study for actively treated patients, i.e. randomized to DL1 or DL2. However, TV1 of the CVT-301-004E study will be used as the baseline for all placebo-treated subjects from study CVT-301-004, for patients from study CVT-301-009, and for patients

	from the observational arm of study CVT-301-005 and other CVT-301 naïve patients. All patients who are enrolled in CVT-301-004E and receive at least 1 dose of CVT-301 will be included in the safety analyses and will be grouped according to the highest dose received. All patients who are enrolled in CVT-301-004E and who receive at least 1 dose of CVT-301 will be included in the efficacy analyses as well but will be grouped according to the randomized treatment. **Safety Analyses** The extent of exposure to study treatment will be summarized for each dose level. For the patients who received CVT-301 treatment in the CVT-301-004 study, the total exposure will be the sum of exposure in the CVT-301-004 study and the CVT-301-004E study. 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. All TEAEs which start after the baseline, as defined above will be included in the analysis. 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 (DL1/DL2 or patients treated with CVT-301/placebo in CVT-301-004) will be estimated using a Mixed Model for Repeated Measurements (MMRM) similar to the one used for the efficacy variables. The proportions of patients meeting ATS quality criteria (and also for those 'rejected') will be summarized. Changes from baseline to follow-up in the rating scales for assessing suicidality, somnolence, and impulse control disorders will be summarized descriptively. For the AWQ, DDS-PC, PHQ-9, Epworth Sleepiness Scale, C-SSRS, and UPDRS Parts 1 and 2, the change from baseline to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 of the withdrawal symptom assessment period will be summarized descriptively. Demographics and baseline characteristics will be summarized descriptively. **Efficacy Analyses** The data for patients who were enrolled in the CVT-301-004 study, the CVT-301-009 study and for the CVT-301-naïve patients study will be primarily analyzed together, while the patients who were enrolled in the CVT-301-003 study will be analyzed separately. A sensitivity analysis will be performed for the patients who enrolled in the CVT-301-004 study separately and for the CVT-301-naïve patients separately. The changes within each dose level and the overall change from baseline in continuous efficacy variables will be estimated using an

	MMRM. Although the focus of this study is to describe the within-group changes, the differences between the dose levels will be estimated as well, but no inferential analyses regarding the between-group differences will be done. The model will include the treatment group (CVT-301 DL1 or CVT-301 DL2), visit, the stratification variables (Hoehn and Yahr disease severity scale rating and screening FEV1 and/or FEV1/FVC) and the interaction between the treatment group and visit as fixed factors. The baseline value will be used as a covariate, if available. The categorical data will be primarily evaluated descriptively. Each visit will be tested separately.

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4. LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	adverse event
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
AWQ	Amphetamine Withdrawal Questionnaire
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
DDS-PC	Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory
DPPC	dipalmitoyl phosphatidylcholine
DBP	diastolic blood pressure
DBS	deep brain stimulation
DL1	Dose Level 1
DL2	Dose Level 2
DLco	carbon monoxide diffusing capacity
DSMB	Data Safety Monitoring Board
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
[redacted]	[redacted]
HR	heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LD	levodopa
LIP	levodopa inhalation powder (CVT-301)
MAO-B	monoamine oxidase-B
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters mercury
MMRM	Mixed Model for Repeated Measurements
MMSE	Mini Mental State Examination
NaCl	sodium chloride
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
PHQ-9	Patient Health Questionnaire
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
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
TEAE	treatment-emergent adverse event
TV1	Treatment Visit 1
TV2	Treatment Visit 2
TV3	Treatment Visit 3
TV4	Treatment Visit 4
TV5	Treatment Visit 5
TV6	Treatment 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).

By avoiding the GI tract, pulmonary delivery of LD has the potential to provide rapid, reliable, and consistent delivery of LD to the systemic circulation and central nervous system, which is expected to translate into reliable and rapid improvement in motor symptoms. 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 Parkinson's disease. CVT-301 will be used as an adjunct to the patient's existing decarboxylase inhibitor (i.e., carbidopa [CD] or benserazide)-inclusive Parkinson's disease 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 (t_{max}) and less variable maximal plasma concentration (C_{max}) compared to oral LD administration. These PK attributes translated to pharmacodynamic advantages in a nonclinical model of Parkinson's disease (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.

[redacted] CVT-301-004E, the present study, is a 14-month extension study in which all patients will receive active treatment, but will remain blinded to dose level. Two inhaled dose levels of CVT-301 (35 mg and 50 mg LD FPD) will be used for treatment of up to 5 OFF episodes per day in PD patients over a 13-month period. Although this is an extension of the CVT-301-004 study, CVT-301-009 patients and CVT-301-naïve patients, including patients who were randomized to the observational arm of study CVT-301-005, may also be enrolled if they meet the CVT-301-004E eligibility criteria. Patients must have completed all of the preceding CVT-301 study visits per protocol without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from the CVT-301-004, CVT-301-005, or CVT-301-009 study prior to completion, *for any reason*, will not be eligible. Patients who received Dose Level 1 (DL1) (35 mg LD FPD) in CVT-301-004 will receive DL1 (35 mg LD FPD) in CVT-301-004E. Patients who received Dose Level 2 (DL2) (50 mg LD FPD) in CVT-301-004 will receive DL2 (50 mg LD FPD) in CVT-301-004E. Patients who received placebo in CVT-301-004, and all former CVT-301-009 patients, as well as CVT-301-naïve patients, will be randomized in 1:1 ratio to DL1 or DL2 in the CVT-301-004E study. Randomization will be differentiated by the

patient's Hoehn and Yahr disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity across each treatment group and by screening spirometry (forced expiratory volume in 1 second [FEV1] <60% of predicted *or* FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% of predicted *and* FEV1/FVC ratio ≥70%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used.

During the 13-month treatment period, patients 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, 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. For the 3 consecutive days prior to Screening Visit 2 (SV2), Treatment Visit 1 (TV1), Treatment Visit 2 (TV2), Treatment Visit 3 (TV3), and Treatment Visit 4 (TV4), Treatment Visit 5 (TV5), and Treatment Visit 6 (TV6) in the PD Diary, patients will record their time asleep and their waking time in different PD states: time OFF, time ON without dyskinesia, time ON with troublesome dyskinesia, and time ON with non-troublesome dyskinesia.

The treatment period has 6 in-clinic visits (TV1, TV2, TV3, TV4, TV5, and TV6). In-clinic efficacy measures include the occurrence and severity of dyskinesia following treatment in the clinic, the 39-Item Parkinson's Disease Questionnaire (PDQ-39), the Patient Health Questionnaire (PHQ-9), the Impact of Parkinson's OFF Episodes Patient Survey, the Patient Global Impression of Change (PGI-C) rating scale, the Schwab and England (S&E) Activities of Daily Living (ADL) score; and UPDRS Part 2 score. In-clinic and at-home efficacy and safety measures will be compared between treatment groups. 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-ead electrocardiograms (ECGs), spirometry, carbon monoxide diffusing capacity (DLco) maneuver, the UPDRS Part 4 (Questions 32-35 and 36-39) score, the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Amphetamine Withdrawal Questionnaire (AWQ), the Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS).

The design of this study, including evaluation of the temporal objective motor responses in-clinic following development of an 'induced' OFF episode after the first morning LD dose is in keeping with studies of other therapeutics that have been developed for treating PD motor fluctuations (Dewey 2001, Grosset 2011).

5.2.1. Rationale for Selection of Doses

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 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 levels that are being studied have been observed to be clinically effective, safe, and tolerated in healthy adult volunteers as well as in PD patients in previously conducted CVT-301 clinical studies. [redacted]

CVT-301 (Levodopa Inhalation Powder)

[redacted]

[redacted]

Clinically, CVT-301 is intended for use as an adjunct to a PD patient's standard oral LD/DDI combination-based regimen. [redacted]

6. STUDY OBJECTIVES

Primary Objective

- To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry (FEV1, FVC, and FEV1/FVC ratio) over a 14-month period.

Secondary Objectives

- 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 PDQ-39.
- Proportion of patients who improved based on the PGI-C rating scale measured pre-dose.
- Change from baseline visit S&E ADL score.
- Change from baseline visit PHQ-9.
- Change from baseline visit Impact of Parkinson's OFF Episodes Patient Survey.
- Change from baseline visit UPDRS Part 2 score.

Safety Objectives:

- To characterize the effects of CVT-301 on safety over a 14-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, the QUIP, the Epworth Sleepiness Scale, the C-SSRS, the AWQ, the DDS-PC, and the self-administered MDS-UPDRS Parts 1B and 2.
- To characterize the effect of CVT-301 on DLco.
- To compare the pulmonary safety, as assessed by spirometry (FEV1 and FEV1/FVC ratio), between the group of patients who were treated with CVT-301 in study CVT-301-004 versus the patients treated with placebo in CVT-301-004.
- Change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Questions 32-35] and wearing off [Questions 36-39]).
- Occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic.

7. INVESTIGATIONAL PLAN

This study is a 14-month, dose-level blinded, multicenter study of 2 inhaled dose levels of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes). The 14 month period includes a 4-week drug holiday to administer withdrawal assessments. All patients will receive active treatment, but patients will be blinded to dose level. This will serve as an extension to the CVT-301-004 study for those patients who participated in that study and remain eligible for this study. In addition, patients who completed study CVT-301-009 per protocol may be enrolled if they meet the CVT-301-004E eligibility criteria. Patients who were randomized to the observational arm of the CVT-301-005 study and completed that study, and other CVT-301-naïve patients may also be enrolled if they meet the CVT-301-004E eligibility criteria. Patients must have completed all of the preceding CVT-301 study visits per protocol without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from the CVT-301-004, CVT-301-005, or CVT-301-009 study prior to completion, *for any reason*, will not be eligible.

Patients who are already enrolled in CVT-301-004E under the prior version of this protocol, including any former CVT-301-003 study patients, will be re-consented to continue in the study under the current amendment. No new patients from the CVT-301-003 study will be permitted to enter the CVT-301-004E study. New patients from CVT-301-004, patients from CVT-301-009, CVT-301-005 observational arm, and other new CVT-301 naïve patients who meet eligibility criteria will be enrolled in CVT-301-004E under the current amendment.

Patients who received CVT-301 in the double-blinded CVT-301-004 study will remain on their same blinded dose level: patients who received DL1 (target nominal dose of 35 mg LD FPD) in CVT-301-004 will receive DL1 (target nominal dose of 35 mg LD FPD) in CVT-301-004E. Patients who received DL2 (target nominal dose of 50 mg LD FPD) in CVT-301-004 will receive DL2 (target nominal dose of 50 mg LD FPD) in CVT-301-004E. Patients who received placebo in CVT-301-004, and all former CVT-301-009 patients, as well as any CVT-301-naïve patients (including patients from the observational arm of CVT-301-005), will be randomized in 1:1 ratio to DL1 or DL2 in the CVT-301-004E study. Randomization will be differentiated by the patient's Hoehn and Yahr disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity across each treatment group and by screening spirometry (forced expiratory volume in 1 second [FEV1] <60% of predicted *or* FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted *and* FEV1/FVC ratio ≥70%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used.

Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode) to deliver the intended dose. Capsules for DL1 and DL2 will appear identical in order to maintain blinding.

The study includes a screening period of up to 35 days (for CVT-301-naïve patients and patients from the CVT-301-009 study) and a treatment period of approximately 13 months. The screening visits are not required for CVT-301-004 patients. CVT-301-004 patients will have a 1- to 14-day period between the last dose of study drug in the CVT-301-004 study and the first dose of study drug in this study. A longer period may be permitted with approval from the Sponsor. Planned visits will occur at 0, and approximately 1, 3, 6, 9, and 14 months.

For CVT-301-naïve patients and patients from study CVT-301-009, spirometry will be assessed at the neurology sites for screening and TV1. The baseline DLco will be performed at dedicated pulmonary sites prior to TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry and DLco after TV1 (within 2 weeks prior to the 3-, 6-, 9-, and 14-month visits, and 4 to 5 weeks following completion of Treatment Visit 6 [TV6]). For patients from CVT-301-004, spirometry will be assessed at the neurology sites at TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry and DLco after TV1 as described for the CVT-301-naïve patients.

For all patients, the treatment period will be approximately 13 months (56±2 weeks) in duration. The maximum anticipated duration of this study for patients from the CVT-301-004 study will be approximately 67 weeks, including the final spirometry and DLco assessment which takes place 4 to 5 weeks following the treatment period. The maximum anticipated duration of this study for CVT-301-naïve patients and CVT-301-009 patients, including the screening period and final spirometry and DLco assessments, will be approximately 72 weeks.

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 the 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.). If a patient has a dose reduction due to tolerability concerns, he/she may be titrated back up to his/her randomized dose (i.e., 2 capsules) at the next scheduled study visit if the investigator determines that the tolerability issue has adequately resolved and the patient could potentially benefit from escalating back up to the original randomized dose level (i.e., 2 capsules). This return to randomized dose may take place at the in-clinic visit or in between visits (if the patient and clinic staff talk by telephone) and may only be done once during the study. Clinic staff will call the patient 1-2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has a tolerability-related dose reduction is re-escalated to the randomized dose and experiences another tolerability issue related to dose level that requires dose reduction, he/she will be dose reduced for a second time and will remain on that dose for the remainder of the study; he/she will not be eligible for any additional up-titration to the original dose.

All patients should continue with their usual prescribed standard PD medication regimen for the study duration. The addition or modification of medications or treatments may include other forms of oral medications **except** oral PRN PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study**.

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 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. There will be no prospective interim evaluation of efficacy endpoint data.

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 11 and in Section 10.1.

8. STUDY POPULATION

CVT-301-004 study patients who have met the eligibility criteria for CVT-301-004 and who have completed all CVT-301-004 study visits per protocol without any safety issues that would preclude participation in this study according to the investigator are eligible for participation in this study. Patients who withdrew from the CVT-301-004 study prior to completion, *for any reason*, will not be eligible.

Additionally, patients from the observational arm of the CVT-301-005 study and patients from the CVT-301-009 study who have completed all prior study visits per protocol and without any safety issues that would preclude participation in this study according to the investigator are eligible for participation in this study if they meet all of the inclusion criteria and if they do not meet any of the exclusion criteria listed below. Patients who withdrew from the CVT-301-005 study or the CVT-301-009 study prior to completion, *for any reason*, will not be eligible.

Other CVT-301-naïve patients must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

8.1. Inclusion Criteria (not assessed for the CVT-301-004 study patients)

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 86 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 disease) 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 MMSE performed in the ON state.

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. Patients with an FEV1/FVC >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 cell transplantation) or plan to have stereotactic surgery during the study period. Patients who have had deep brain stimulation [DBS] will also be excluded unless the procedure was performed more than 6 months prior to study enrollment.

5. Patients with a history of psychotic symptoms requiring treatment, or suicidal ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of

anti-depressant medications 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 15 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 unable to comply with study procedures or make them unsuitable for participation in the study.
13. Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety. Potential issues of concern should be raised to the medical monitor during eligibility review.
14. For new CVT-301 naïve patients, 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).

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 (TV1) (the screening period may be extended for up to 2 weeks to accommodate this recovery).

8.3. Removal of Patients from Study

A patient will be considered to have completed the study (and be considered a 14-month completer) when he or she has completed all study visits up to and including TV6. A patient will be considered to be a 6-month completer if he/she completes all study visits up to and including TV4. 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 TV6 and post-TV6 assessments as shown Appendix 10 and Appendix 11. 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, 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 Treatments

Basic information about the study drugs is provided in Table 1.

Table 1 Details of Study Drug

	CVT-301 (Test Product)
Name	CVT-301 (levodopa inhalation powder)
Manufacturer	Civitas Therapeutics, Inc.
Doses	DL1: 2 CVT-301 capsules delivering a target nominal respirable dose of approximately 35 mg LD FPD DL2: 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	**DL1 capsule units:** Capsule fill weight of LD: 30 mg Respirable LD dose/FPD per capsule: 17.5 mg (Emitted LD per capsule: 25 mg) **DL2 capsule units:** Capsule fill weight of LD: 42 mg Respirable LD dose/FPD per capsule: 25.0 mg (Emitted LD per capsule: 35 mg)

Abbreviations: DL1=Dose Level 1; DL2=Dose Level 2; FPD=fine particle dose; LD=levodopa.

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

[redacted]

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 [redacted] 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 DL1 and CVT-301 DL2 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 Blinded 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 randomized patient 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.

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, or send an email to the Quality Clinical Complaints mailbox: [redacted] 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, Blinding, and Administration of Study Treatment

9.2.1. Randomization and Assignment of Study Treatment

Following completion of SV2 and prior to randomization (for CVT-301-009, CVT-301-005 and other CVT-301-naïve patients), eligibility criteria will be reviewed by delegated staff to confirm eligibility. Sites must leave a minimum of 5 days between randomization and Treatment Visit 1.

Before TV1, patients will be assigned/randomized to treatment. Patients who received DL1 (target nominal dose of 35 mg LD FPD) in the CVT-301-004 study will receive DL1 (target nominal dose of 35 mg LD FPD) in this study, and patients who received DL2 (target nominal dose of 50 mg LD FPD) in the CVT-301-004 study will receive DL2 (target nominal dose of 50 mg LD FPD) in this study.

Patients who received placebo in the CVT-301-004 study, CVT-301-009 patients, and CVT-301-naïve patients (including CVT-301-005 observational arm patients) will be randomized in a 1:1 ratio to DL1 or DL2. Upon confirmation of eligibility, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). Randomization will be differentiated by the patient's Hoehn and Yahr PD disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity 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%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used. Patients and site staff will be blinded to treatment level.

9.2.2. Distributing Blinded Inhaled Study Treatment

Prior to the self-administration of inhaled study treatment, study staff will ensure that patients are adequately trained on the use of the inhaler according to the IFU. The IFU will be provided to each patient and will be part of the permanent study record.

In order to blind the study treatment, study kits with identical number and appearance of capsules will be distributed to patients in the DL1 and DL2 groups.

The patient, investigator, study site personnel, the Sponsor, and representatives of the contract research organization (CRO) involved in monitoring, data management, or other aspects of the study, and Core Laboratories will be blinded to the inhaled study treatment.

Except in the case of an emergency, the study treatment codes will not be available to the investigator, the study site personnel, representatives of the CRO, or the Sponsor until after the completion of the study and final data review. All randomization data will be kept strictly confidential and accessible only to authorized persons until the time of unblinding after the end of the study; for emergency unblinding, the site will access the IWRS or call the IWRS helpdesk. When the data file has been verified and the protocol violations have been determined, the drug codes will be made available for data analysis.

9.2.3. Defining "Time 0" (T0)

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 in the clinic and at home, "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 reinhaled, T0 is at the end of the reinhalation administration.

9.3. Treatment Accountability and Compliance

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

For CVT-301-naïve patients and patients from the CVT-301-009 study, 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 CVT-301-naïve patients and former CVT-301-009 patients 4-6 days prior to TV1 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 TV1. 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.

For CVT-naïve patients and patients from the CVT-301-009 study, medications taken by or administered to the patient for 3 months prior to SV1 will be recorded in the eCRF. These patients must be stable on oral LD-containing therapy which 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). This regimen must have been stable for at least 2 weeks prior to SV1 when not including Rytary, and stable for at least 6 weeks prior to SV1 when including Rytary,

During the study, all patients' standard PD medication regimens may be altered if needed to manage PD symptoms. The addition or modification of medications or treatments may include other forms of oral medications **except** oral PRN PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study**.

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, or other non-LD-containing PD medications, 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, the dose must be stable for at least 4 weeks prior to SV1.

Patients who may be using medical marijuana as a treatment for their PD in states where the use of marijuana is legal for medical purposes 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.).

Patients meet all other eligibility criteria (including spirometry).

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 standard PD medications during the study including on the morning of each in-clinic treatment 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, 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 patient will resume their standard schedule of PD medications.

At home, patients should maintain their usual schedule of standard oral PD medications, in addition to using the inhaled study drug for the treatment of OFF episodes. Patients should not take inhaled study drug within 45 minutes following their prior dose of standard oral PD medication. 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 should not take oral PRN PD medications to manage their OFF states throughout the treatment period.

Standard Prescribed Oral PD Medication Use for Prolonged OFF Episodes

In the clinic, 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 standard oral dose of PD medication 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, patients will be permitted to take their next scheduled dose of their standard prescribed PD medication; patients may not re-dose with inhaled study drug for that 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, and they may not take additional inhaled study medication.

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. Patients must not have used apomorphine for at least 4 weeks prior to SV1 and must not use apomorphine for the duration of the study.
- 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 visits).
- Oral PRN PD medications during the treatment period. CVT-301-naïve patients and CVT-301-009 patients are permitted to take oral PRN PD medications during the screening period and during the study drug holiday. However, *oral PRN PD medications are not permitted during the treatment period while taking study medication.*

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 visits are provided in Appendix 2 through Appendix 11. Unless otherwise specified, all assessments will be performed by the investigator or other assigned personnel.

10.1. Assessments by Visit

Assessments are to be performed as outlined in the following by-visit subsections. Study assessments are also outlined in the Appendix 2 through Appendix 11.

10.1.1. Screening Period

CVT-301-004 patients will not be required to undergo the screening visits and will undergo TV1 after a 1- to 14-day period (or longer if approved by the Sponsor) following TV4 of the CVT-301-004 study.

CVT-301-naïve patients (including CVT-301-005 observational arm patients) and patients from the CVT-301-009 study will undergo a screening period of up to 35 days before randomization. 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 TV1 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.

10.1.1.1. Screening Visit 1 for CVT-301-Naïve Patients and CVT-301-009 Patients (within 35 days prior to randomization)

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 14.)
5. Use the modified Hoehn and Yahr scale to assess PD severity (in an ON state). (Refer to Appendix 15.)
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 Parts 1, 2, 3 and 4 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. Take samples for clinical laboratory tests, including a serum pregnancy test for females of childbearing potential (see Appendix 13 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)
18. Introduce the inhaler and perform inhaler training using sham capsules with the CVT-301 inhaler while in the ON state.
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.

10.1.1.2. Screening Visit 2 for CVT-301-Naïve Patients and CVT-301-009 Patients (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.
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 TV1.
7. 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 Parts 1, 2 and 4 (in an ON state); 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).
8. Complete the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in an ON state).
9. Monitor for AEs throughout the visit.

10. Schedule a DLco assessment to be performed at an outside pulmonary laboratory after SV2 and prior to TV1. 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.

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 TV1 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 TV1 and that they should contact the site if an intervening illness occurs prior to TV1. 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.

10.1.2. Randomization to Study Drug

Following completion of SV2 and prior to randomization (for CVT-301-naïve patients and CVT-301-009 patients), eligibility criteria will be reviewed by the external reviewer (subjects requiring pulmonary adjudication may not be randomized until completion of pulmonologist reviewer).

Before TV1, patients will be assigned/randomized to treatment. Patients who received DL1 (target nominal dose of 35 mg LD FPD) in the CVT-301-004 study will receive DL1 (target nominal dose of 35 mg LD FPD) in this study, and patients who received DL2 (target nominal dose of 50 mg LD FPD) in the CVT-301-004 study will receive DL2 (target nominal dose of 50 mg LD FPD) in this study. Patients who received placebo in the CVT-301-004 study, CVT-301-009 patients, and CVT-301-naïve patients (including those from CVT-301-005 observational arm) will be randomized in a 1:1 ratio to DL1 or DL2. If a patient meets final eligibility requirements, eligibility will be reviewed by delegated staff. Randomization will be differentiated by the patient's Hoehn and Yahr disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity 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%). For the patients who received placebo in CVT-301-004, the differentiation of CVT-301-004 will be used. Patients and site staff will be blinded to treatment level. Site staff must allow at least 5 days between date of randomization in the IWRS and the date of TV1.

Refer to Section 9.2 for further randomization details.

10.1.3. Treatment Period

The assessments and procedures performed at TV1 will differ for patients entering from the CVT-301-004 study than for CVT-301-naïve patients (including those from CVT-301-005 observational arm) and prior CVT-301-009 patients.

All patients, regardless of treatment assignment, should continue with their usual prescribed standard PD medication regimen for the study duration. This regimen may be altered if needed

during the course of the 14-month study. The addition or modification of medications or treatments may include other forms of oral medications **except** oral PRN PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study**.

The treatment period includes 6 separate in-clinic 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.

During this period, patients will self-administer inhaled study treatment (CVT-301 DL1 or CVT-301 DL2) up to 5 times daily to treat OFF episodes during their waking day. The first dose of blinded study drug will be given in the clinic at TV1 (i.e., 2-capsule inhalations per dose of either CVT-301 DL1 or CVT-301 DL2); patients will be given study drug kits at TV1, TV2, TV3, TV4, and TV5.

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 the 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.). If a patient has a dose reduction due to tolerability concerns, he/she may be titrated back up to his/her randomized dose (i.e., 2 capsules) at the next scheduled study visit if the investigator determines that the tolerability issue has adequately resolved and the patient could potentially benefit from escalating back up to the original randomized dose level (i.e., 2 capsules). This return to randomized dose may take place at the in-clinic visit or in between visits (if the patient and clinic staff talk by telephone) and may only be done once during the study. Clinic staff will call the patient 1-2 days after the dose escalation to see if the patient has any questions or concerns. If a patient who has a tolerability-related dose reduction is re-escalated to the randomized dose and experiences another tolerability issue related to dose level that requires dose reduction, he/she will be dose reduced for a second time and will remain on that dose for the remainder of the study; he/she will not be eligible for any additional up-titration to the original dose.

Refer to Appendix 2 through Appendix 11 for tables of study assessments at each visit during the treatment period.

10.1.3.1. Telephone Calls Before Treatment Visits

- Pre TV1 call:
  - Call the CVT-301-naïve patients and CVT-301-009 patients within 4-6 days before TV1 for the following reasons: to confirm the DLco assessment has been

done or is scheduled to occur before TV1 (can be done any time after SV2); to confirm the next study visit; 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 the CVT-301-naïve patients and CVT-301-009 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 TV1. 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.

- Post TV1 call:
  - Call the patients 1 to 3 days after TV1 to address any potential concerns or challenges with the inhaler systems or Inhaled Dosing Log.
- Pre TV2, TV3, and TV4 calls:
  - Call the patients 1 week 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 that the DLco and spirometry visit at the pulmonary function lab has been done or is scheduled to occur (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.

10.1.3.2. Treatment Visit 1 for CVT-301-004 Patients (1-14 days after TV4 in the CVT-301-004 study)

Informed consent will be obtained prior to receiving drug for this extension study. Patients should provide written informed consent for this study at TV4 of the CVT-301-004 study.

Patients will be instructed to take their prescribed oral PD medications on their usual schedule. The timing of arrival for TV1 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 of their usual PD medications.

On Arrival to the Clinic

The following list is a suggested schedule for this visit:

- Record the usual PD medication dose/regimen.
- Record the time that patients took their usual PD medications prior to the visit.
- Record all concomitant medications.
- Perform a full physical examination.
- Patient will complete the PHQ-9 in an ON state.
- Patient will complete the AWQ and DDS-PC in an ON state.
- Perform a 12-lead ECG (as described in Section 11.1.3).
- Record standard and orthostatic BP and HR (see Section 11.1.2). 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.
- Complete the C-SSRS and Epworth Sleepiness Scale, (preferably in the ON state).
- Complete the UPDRS Parts 1 and 2 (preferably in the ON state).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Re-train patients on the proper use of the inhaler with sham capsules, including a review of the IFU.
- Distribute the PD Diary and review instructions 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 TV6).
- Distribute the Inhaled Dosing Log and review instructions 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 13-month treatment period).
- Distribute study drug kits to patients.

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 blinded study drug from the study drug kits that were provided (i.e., 2 capsule inhalations of either CVT-301 DL1 or CVT-301 DL2). Patients will be permitted sips of water between capsule inhalations as needed.

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 17 for additional system information.

Post-dose (10 – 60 minutes)

After dosing, patients will undergo serial safety evaluations. Refer to Appendix 4 for the detailed time and events table. 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.
- Evaluate spirometry at 15, 30, and 60 minutes post-dose. At the time of each spirometry assessment, clinic staff will record the patient's motor state. If within the first 60 minutes after inhalation, the patient's spirometry assessment shows either of the following, the patient will NOT be sent home with study drug, and the site will follow the Spirometry Alert and Review Process: a decrease in FEV1 ≥ 20% AND a decrease in FEV1 by 200 mL compared with pre-dose results, and/or a reduction in the FEV1/FVC ratio to <60%. If either criteria are met, the patient will NOT be sent home with study drug and the procedures described in Appendix 18 will be followed.
- 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). Clinic staff will arrange to speak with patients by telephone 1 to 3 days after TV1 to monitor for AEs and to address any potential concerns or challenges with the inhaler systems or Inhaled Dosing Log. The next visit will be scheduled. Additionally, clinic staff will arrange to speak with patients by telephone 1 week 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 and spirometry visit at the pulmonary function lab 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).

10.1.3.3. Treatment Visit 1 for CVT-301-Naïve Patients and CVT-301-009 Patients (at least 7 days after SV2)

Patients will complete the PD Diary and the Screening ON/OFF Episodes Log 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 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 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 at the pulmonary lab. 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.
- Patient will complete the PDQ-39 and PHQ-9 in an ON state.
- Patient will complete the AWQ and DDS-PC in an ON state.
- Perform a brief physical examination.
- Complete the UPDRS Parts 1 and 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- 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 C-SSRS, Epworth Sleepiness Scale, and the QUIP (preferably in the ON state).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Re-train patients on the proper use of the inhaler with sham capsules, including a review of the IFU.
- 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 TV6).
- 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 13-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.

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 blinded study drug from the study drug kits provided (i.e., 2 capsule inhalations of either CVT-301 DL1 or CVT-301 DL2). Patients will be permitted sips of water between capsule inhalations as needed.

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 17 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.
- Evaluate spirometry at 15, 30, and 60 minutes post-dose. At the time of each spirometry assessment, clinic staff will record the patient's motor state. If within the first 60 minutes after inhalation, the patient's spirometry assessment shows either of the following, the patient will NOT be sent home with study drug, and the site will follow the Spirometry Alert and Review Process: a decrease in FEV1 $\geq$ 20% AND a decrease in FEV1 by 200 mL compared with pre-dose results, and/or a reduction in the FEV1/FVC ratio to <60%. If either criteria are met, the patient will NOT be sent home with study drug and the procedures described in Appendix 18 will be followed.
- 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 TV1 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 1 week 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 and spirometry visit at the pulmonary function lab 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).

10.1.3.4. At-Home Dosing

At TV1, TV2, TV3, TV4, and TV5, patients will receive study drug kits and the IFU to take home with them, except during the study drug holiday. Patients will also receive study drug kits and the IFU to take home with them at TV4.1, TV5.1, or at an Unscheduled Visit. Patients will be instructed to continue with their usual prescribed standard PD medication regimen for the study duration. This regimen may be altered if needed during the course of the 14-month study. The addition or modification of medications or treatments may include other forms of oral medications **except** oral PRN PD medications while taking study medication. During the study drug holiday, patients are allowed to take oral PRN PD medication to manage their 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. The total daily LD dose of the modified PD regimen (not including CVT-301) must not exceed 1600 mg per day while taking study medication. **Apomorphine is not permitted during the study**.

Any modifications to the standard PD dose and/or regimen will be recorded in the eCRF.

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. Patients may not take oral PRN medications to manage OFF states during the treatment period.

> *Note: If Study CVT-301-009 supports the safety and tolerability of CVT-301 administration in the early morning, investigators will be informed that participants in the current study CVT-301-004E can start to take study drug for early morning OFF periods. Until that time study drug may **not** be used to treat morning akinesia.

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 oral 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 13-month treatment period, excluding the study drug holiday. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV1 and 1 week prior to each visit for TV2, TV3,

TV4, TV5, and TV6.Patients will bring the PD Diary, Inhaled Dosing Log, and used supplies, including empty capsules and inhalers, as well as any unused supplies to the clinic visit.

10.1.3.5. Treatment Visit 2 for all Patients (1 month [4 weeks ±5 days] after TV1)

Patients will complete the PD Diary for the 3 consecutive days prior to TV2, and patients will complete 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.
- Patient will complete the PDQ-39, PHQ-9, and PGI-C in an ON state.
- Complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- 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 the C-SSRS, Epworth Sleepiness Scale, and the QUIP (preferably in the ON state).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Distribute new study drug kits.
- Review inhaler training with the patient.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.

- 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. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1 or CVT-301 DL2).
- Observe the patient for the appearance of dyskinesia and note in the source record if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of the dyskinesia.
- 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.
- 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.
- 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 also schedule the DLco and spirometry visit within 2 weeks prior to TV3. These assessments 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. Clinic staff will arrange to speak with patients by telephone 1 week 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 and spirometry visit at the pulmonary function lab 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).

10.1.3.6. Treatment Visit 3 for all Patients (3 months 12±2 weeks after TV1)

Patients will complete the PD Diary for the 3 consecutive days prior to TV3, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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 and spirometry visit at the pulmonary function lab was performed within 2 weeks prior to TV3. If these assessments were not 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.
- Patient will complete the PDQ-39, PHQ-9, and PGI-C scale in an ON state.
- Complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in the ON state).
- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Perform a 12-lead ECG.
- 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 (if needed).
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
- 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. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1 or CVT-301 DL2).
- Observe the patient for the appearance of dyskinesia and note in the source record if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of the dyskinesia.
- 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.

- 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.
- 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 also schedule the DLco and spirometry visit within 2 weeks prior to TV4. These assessments 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. Clinic staff will arrange to speak with patients by telephone 1 week 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 and spirometry visit at the pulmonary function lab 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).

10.1.3.7. Treatment Visit 4 for all Patients (6 months [24±2 weeks] after TV1)

Patients will complete the PD Diary for the 3 consecutive days prior to TV4, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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 (also refer to Section 10.1.4 for patients entering the study drug holiday and withdrawal sub-study):

- 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 and spirometry visit at the pulmonary function lab was performed within 2 weeks prior to TV4. If these assessments were not 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.
- Patient will complete the PDQ-39, PHQ-9, and PGI-C scale in an ON state.

- Complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in the ON state).
- Perform a full physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Perform a 12-lead ECG.
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Distribute new study drug kits for patients not entering the study drug holiday.
- Review inhaler training with the patient (if needed) for patients not entering the study drug holiday.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion for patients not entering the study drug holiday.
- 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. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1 or CVT-301 DL2).
- Observe the patient for the appearance of dyskinesia and note in the source record if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of the dyskinesia.
- 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.
- 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 for patients not entering the study drug holiday.
- 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 for patients not entering the study drug holiday).

The next visit will be scheduled. Clinic staff will also schedule the DLco and spirometry visit at the pulmonary function lab within 2 weeks prior to TV5. These assessments 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. Clinic staff will arrange to speak with patients by telephone 1 week 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 and spirometry visit at the pulmonary function lab 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).

10.1.3.8. Treatment Visit 5 for all Patients (9 months [36±2 weeks] after TV1)

Patients will complete the PD Diary for the 3 consecutive days prior to TV5, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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 (also refer to Section 10.1.4 for patients entering the study drug holiday and withdrawal sub-study):

- 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 and spirometry visit at the pulmonary function lab was performed within 2 weeks prior to TV5. If these assessments were not 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.
- Patient will complete the PDQ-39, PHQ-9, and PGI-C scale in an ON state.
- Complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in the ON state).

- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Perform a 12-lead ECG.
- Collect blood for clinical laboratory tests including serum pregnancy test, if applicable. Document fasting status.
- Distribute new study drug kits for patients not entering the study drug holiday.
- Review inhaler training with the patient (if needed) for patients not entering the study drug holiday.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion for patients not entering the study drug holiday.
- 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. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1 or CVT-301 DL2).
- Observe the patient for the appearance of dyskinesia and note in the source record if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of the dyskinesia.
- 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.
- 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 for patients not entering the study drug holiday.
- 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 for patients not entering the study drug holiday).

The next visit will be scheduled.*Clinic staff will also schedule the DLco and spirometry visit within 2 weeks prior to TV6. These assessments 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. Clinic staff will arrange to speak with patients by telephone 1 week 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 and spirometry visit at the pulmonary function lab

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).

*Patients who have already completed TV5 at the time of implementation of protocol Version 5.2 will have the option to consent to this amendment at an Unscheduled Visit prior to TV6, at which time they will receive an additional 4 weeks of study drug so that TV6 can be scheduled for approximately 13 months (56±2 weeks) after TV1. These patients will participate in the withdrawal sub-study post-TV6 as described in Section 10.1.4.

10.1.3.9. Treatment Visit 6 for all Patients (13 months [56±2 weeks] or 14 months (60 ±2 weeks) after TV1)/Early Withdrawal Visit

Treatment Visit 6 will constitute the end-of-study visit. Patients will complete the PD Diary for the 3 consecutive days prior to TV6, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They 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 (also refer to Section 10.1.4 for patients entering the withdrawal sub-study):

- 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 and spirometry visit at the pulmonary function lab was performed within 2 weeks prior to TV6. If these assessments were not 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.
- Patient will complete the PDQ-39, PHQ-9, and PGI-C scale in an ON state.
- Complete the UPDRS Part 2 and S&E ADL scales (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in the ON state).

- Perform a brief physical examination.
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Patient will complete the Impact of Parkinson's OFF Episodes Patient Survey (preferably in an ON state)
- Perform a 12-lead ECG.
- 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. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1 or CVT-301 DL2).
- Observe the patient for the appearance of dyskinesia and note in the source record if the patient experiences dyskinesia at any time within the 60-minute post-dose period. Also, if applicable, record the maximum severity of the dyskinesia.
- 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 and spirometry visit at the pulmonary lab 4 to 5 weeks after completion of TV6. These assessments 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.

10.1.4. Sub-Study to Assess Potential Withdrawal Symptoms

After patients are consented to protocol Version 5.2, they will participate in a withdrawal symptom sub-study at the end of TV4, TV5, or TV6, depending on which of the visits is the next scheduled one for the patient. In addition to the assessments detailed in the previous sections for the treatment visit, the AWQ and DDS-PC will be performed upon arrival in the ON state, and the UPDRS Part 1 will be performed preferably in the ON state.

When study activities for the visit are completed, patients will begin a 28-day period of assessment of potential drug withdrawal symptoms. To this end, patients who are at TV4 or TV5 at the time of consent will go on a study drug holiday for this time period. All patients in the withdrawal sub-study (patients consented to protocol Version 5.2) will be given copies of the AWQ, the DDS-PC, PHQ-9, Epworth Sleepiness Scale, C-SSRS (self-report version), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS) to be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after the treatment visit. Patients should fill out the questionnaires during their first ON state (after the intake of their first scheduled dose of standard oral PD medication) on each of these days. The site will call patients

at 14 (±3) days after the treatment visit to remind them to complete the questionnaires, and to inquire about potential adverse events and changes in concomitant medications. Patients who enter the withdrawal sub-study after TV6 will also receive a call at 28 (±3) days.

Patients who entered the study drug holiday will be scheduled to return to the clinic for a drug re-supply visit (see Section 10.1.4.1), and resumption of the full course of study treatment. Patients who entered the withdrawal sub-study after TV6 will be completed with the study after they return the questionnaires and undergo the DLco and spirometry assessment 4 to 5 weeks after completion of TV6, as described in Section 10.1.3.9.

10.1.4.1. Treatment Visit 4.1/5.1 (28 days+1 week after TV4 or TV5)

The following procedures will be performed at the drug re-supply visit to be scheduled at the conclusion of the patient's study drug holiday:

- Collect completed questionnaires
- Record any changes in the usual PD medication dose/regimen.
- Record any changes in concomitant medications.
- Record any adverse events.
- Distribute new study drug kits.
- Review inhaler training with the patient (if needed).
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion

10.1.5. Early Withdrawal Visit

Patients who withdraw prematurely will complete the TV6 assessments (see Section 10.1.3.9), except for the pre-TV6 DLco and spirometry assessments, at the time of withdrawal. In addition, patients will be scheduled the DLco and spirometry visit 4 to 5 weeks after completion of the Early Withdrawal Visit. The DLco and spirometry assessments 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. Patients who withdraw prematurely and prior to participating in the sub-study to assess potential withdrawal symptoms will complete the withdrawal assessments during the 28 days following completion of the TV6 assessments (see Section 10.1.4).

10.1.6. Unscheduled Visits

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

- For CVT-301-naïve patients, 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.

- For CVT-301-naïve patients, 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.).
- Patients who have completed TV5 at the time of implementation of protocol Version 5.2 will have the option to consent to this amendment at an Unscheduled Visit prior to TV6, at which time they will receive an additional 4 weeks of study drug so that TV6 can be scheduled for approximately 13 months (56±2 weeks) after TV1.

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, impulse control disorders, and withdrawal symptoms 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 10. Genital, rectal, and breast examination may be excluded if not clinically indicated. The physical examination will include height (cm) and weight (kg) only at screening. 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 10. 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 10 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 13. 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 [redacted] 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) for CVT-301-naïve patients and CVT-301-009 patients, and at TV1, TV3, TV4, TV5, and TV6, 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 and at dedicated pulmonary function facilities:

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 collected by the study sites will reviewed by a central spirometry laboratory [redacted] 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). FEV_1, FVC and FEV_1/FVC ratio will be recorded from the single "best test" (based on effort with highest summed FEV_1 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. 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/European Respiratory Society (ERS) criteria. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization. Any CVT-301-naïve patients or CVT-301-009 patients requiring pulmonary adjudication at screening will not be randomized until after full pulmonologist review.

Spirometry assessments will be done at the time points indicated in Appendix 2 through Appendix 10. 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 for CVT-301-naïve patients and CVT-301-009 patients at SV1, SV2 (if necessary) and TV1 (all patients). All other spirometry assessments will be collected during the DLco and spirometry visits that take place at the pulmonary function lab. Spirometry data collected at pulmonary function labs will be reviewed immediately by a pulmonologist on site for safety signals and then sent to and reviewed by a central Pulmonary Function Testing reviewer (TechEd Consultants).

11.1.7. Carbon Monoxide Diffusing Capacity (diffusing capacity of the lungs for carbon monoxide-DLco)

Patients will undergo DLco assessments, which will be acquired in accordance with ATS criteria (Miller et al., 2005), at a dedicated pulmonary function facility after SV2 (and prior to TV1; 301-naïve patients and CVT-301-009 patients), within 2 weeks prior to TV3, TV4, TV5, and TV6, and at 4 to 5 weeks after TV6, as described in the Appendix 3 through Appendix 10. These assessments should be performed while the patient is in the ON state (as reported by the patient to the pulmonary technician). Pulmonary function facility technicians will perform a slow vital capacity maneuver, followed by DLco, and then spirometry. The pulmonary facilities will use

their own equipment to perform all necessary pulmonary function testing relevant to DLco acquisition.

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 (defined as SV1 of the CVT-301-004E study for CVT-301-naïve and CVT-301-009 patients and SV1 of the CVT-301-004 study for CVT-301-004 patients) and new symptoms, physical signs, syndromes, or diseases should be noted on the AE page of the eCRF during the study. For these AEs captured on the AE eCRF for CVT-301- naïve and CVT-301-009 patients, AEs reported prior to the first study treatment at TV1 will be considered baseline AEs, and AEs reported from first treatment 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 2 and Table 3, respectively.

Table 2 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 3 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. [redacted]

[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 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 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 as indicated in the time and events tables in Appendix 2 through Appendix 10. The baseline assessment for CVT-301-naïve and CVT-301-009 patients will be completed at TV1. The baseline assessment for CVT-301-004 patients will have been completed at TV1 of CVT-301-004 study.

Additionally, during the post-dosing follow-up period at TV2, TV3, TV4, TV5, and TV6, the examiner will observe the patient for the appearance of dyskinesia during the 60-minute post-dose period and the maximum severity (mild, moderate, or severe) of any dyskinesia in the 60-minute post-dose period will be noted in the eCRF. 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-Suicide 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. For CVT-301-naïve and CVT-301-009 patients, an initial baseline version will be given at SV2, and for all patients, a "since last visit" version will be given at all treatment visits to detect any emergence of suicidal ideation or behavior. CVT-301-004 patients will have completed the baseline version during TV1 of the CVT-301-004 study. The clinic staff should address any emerging neuropsychiatric needs in the event that the C-SSRS indicates active suicidal ideation.

Additional assessments of the C-SSRS will be completed as indicated in the time and events tables in Appendix 4 through Appendix 10. The self-report version of the C-SSRS will be completed at home during the withdrawal assessment period.

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 for CVT-301-naïve patients and CVT-301-009 patients will be completed at TV1 of this study. The baseline assessment for CVT-301-004 patients will have been performed at TV1 of the CVT-301-004 study (except for assessment of withdrawal symptoms). As described in Appendix 3 through Appendix 10, additional assessments will be completed at TV2, TV3, TV4, TV5, and TV6 (or Early Withdrawal, if applicable), and post-TV6.

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 for CVT-301-naïve patients and CVT-301-009 patients will be completed at TV1 of this study. The baseline assessment for CVT-301-004 patients will have been performed at TV1 of the CVT-301-004 study. As described in Appendix 4 through Appendix 10, additional assessments will be completed at TV2, TV3, TV4, TV5, and TV6 (or Early Withdrawal, if applicable).

11.1.12.5. Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC)

The DDS-PC inventory is used to help identify patients who experience impulsive-compulsive behaviors associated with dopamine dysregulation syndrome. Patients will complete the questionnaire upon arrival at the clinic in an ON state at TV1 and at the visit at which the withdrawal assessment period begins (TV4, TV5, TV6 or Early Withdrawal). Additional assessments will be completed in an ON state at home during the withdrawal assessment period at the time points indicated in Appendix 8 through Appendix 10.

11.1.12.6. Amphetamine Withdrawal Questionnaire (AWQ)

The AWQ will be completed by patients to assess potential withdrawal symptoms. Patients will complete the scale upon arrival at the clinic in an ON state at TV1 and at the visit at which the withdrawal assessment period begins (TV4, TV5, TV6 or Early Withdrawal). Additional assessments will be completed in an ON state at home during the withdrawal assessment period at the time points indicated in Appendix 8 through Appendix 10.

11.2. Efficacy Assessments

Efficacy will be evaluated from both in-clinic and at-home assessments, as outlined by the following criteria:

In-Clinic Criteria:

- 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
- PDQ-39
- PHQ-9
- Impact of Parkinson's OFF Episodes Patient Survey
- PGI-C
- S&E ADL
- UPDRS Part 2

At-Home Criteria:

- 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.

11.2.1. Assessment of ON and OFF States and Dyskinesia

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

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 TV1 (for CVT-301-naïve and CVT-301-009 patients), and TV2, TV3, TV4, TV5, and TV6, patients 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).

New diaries will be distributed at each study visit, except for TV6, 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)

The CVT-301-naïve patients and CVT-301-009 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 TV1. These logs will be distributed at SV1 and SV2, and patients will bring the completed logs to the clinic at SV2 and TV1. Information in the logs will be reviewed and recorded by clinic staff.

11.2.1.2.3. Inhaled Dosing Log (for the Treatment Period)

Every day during the treatment period, patients 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 TV1, TV2, TV3, TV4, and TV5, and patients will bring the completed logs to the clinic at TV2, TV3, TV4, TV5, and TV6. Information in the logs will be reviewed and recorded by clinic staff.

11.2.2. UPDRS Part 3

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 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

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 in the ON state as indicated in the time and events tables in Appendix 5 through Appendix 10. The baseline assessment for CVT-301-naïve and CVT-301-009 patients will be completed at TV1. The baseline assessment for CVT-301-004 patients will have been completed at TV1 of CVT-301-004 study.

11.2.4. PHQ-9

The PHQ-9 is the nine item self-report depression scale of the Patient Health Questionnaire which incorporates the nine diagnostic criteria for major depressive disorder in the DSM-IV (Diagnostic and Statistical Manual Fourth Edition). Patients are asked to rate the frequency of symptoms on a scale of 0 ("not at all") to 3 ("nearly every day"). The PHQ-9 is used to characterize affective and motivational states (apathy) in these patients.

The PHQ-9 will be completed in the ON state as indicated in the time and events tables in Appendix 4 through Appendix 10, including during the withdrawal assessment period at home.

11.2.5. PGI-C

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 will be completed in the ON state as indicated in the time and events tables in Appendix 6 through Appendix 10. The extent of change will be determined in relation to when the patient first received active study medication.

11.2.6. Impact of Parkinson's OFF Episodes Patient Survey

The Impact of Parkinson's Off Episodes Patient Survey is a survey for patients with PD to report on their symptom management with medications. Patients will complete the survey at all treatment visits or the Early Termination visit, if applicable.

11.2.7. Schwab & England Activities of Daily Living

The S&E ADL scale will be completed by a qualified rater upon arrival as indicated in the time and events tables in Appendix 5 through Appendix 10, preferably while the patient is in the ON state. The baseline assessment for CVT-301-naïve and CVT-301-009 patients will be completed at TV1. The baseline assessment for CVT-301-004 patients will have been completed at TV1 of CVT-301-004 study.

11.2.8. UPDRS Part 2 and MDS-UPDRS Part 2

The UPDRS Part 2 is an evaluation of the ADL; this will be assessed by a qualified rater as indicated in the time and events tables in Appendix 2 through Appendix 10, preferably while the patient is in the ON state. The baseline assessment for CVT-301-naïve and CVT-301-009 patients will be completed at TV1. The baseline assessment for CVT-301-004 patients will have been completed at TV1 of CVT-301-004 study (except for assessment of withdrawal symptoms). The self-administered MDS-UPDRS Part 2 will be completed at home during the withdrawal assessment period (see Appendix 8 through Appendix 10).

11.3. Other Assessments Used for Baseline Disease Characteristics

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 14 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 15).

11.3.3. UPDRS Part 1 and MDS-UPDRS Part 1B

The UPDRS Part 1 assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living, and will be performed at SV1 as part of the baseline characterization of the patient (not used to determine eligibility). Additionally, it will be performed at TV1 and at the visit at which the withdrawal assessment period begins (TV4, TV5, TV6 or Early Withdrawal), The self-administered MDS-UPDRS Part 1B will be completed at home during the withdrawal assessment period (see Appendix 8 through Appendix 10).

11.3.4. 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.

11.3.5. Pulmonary Function Baseline Questionnaire

The patient's pulmonary history will be recorded by completing the Pulmonary Function Baseline Questionnaire at SV1 of this study for CVT-301-naïve and CVT-301-009 patients and at SV1 of the CVT-301-004 study for CVT-301-004 patients. 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. Optional Videotaping at Select Study Sites

At select study sites, and in compliance with all applicable country-specific, state, and local laws and regulations, patients may be invited to participate in a videotaping of the inhaled medication dosing procedure and some specified study procedures. These videos will be used by the Sponsor for purposes of reviewing and improving the dosing procedure. Additionally, the videos may be used for educational and demonstration purposes for Sponsor staff, regulatory authorities, patients, nurses, and physicians. Any potential identifying features will be blurred in any final video reproduction that is prepared. If a selected study site does not possess the capabilities to perform the videography, a third-party company will manage the videotaping. Patients who agree to be videotaped and/or photographed will sign a separate consent form.

11.5. 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 scales and C-SSRS 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 PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire. 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 dose group.

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. The SAP may be updated during the conduct of the study and will be finalized before the data base lock. However, the analyses defined after the blind of study CVT-301-004 has been broken will be considered as exploratory.

12.1. Determination of Sample Size

The study is planned is to enroll approximately 390 patients to ensure that approximately 290 patients will complete the 12 month study. All patients who completed the CVT-301-004 and the CVT-301-009 study per protocol without any safety issues are eligible. In addition, CVT-301-naïve patients, including those who participated in the CVT-301-005 observational arm may be enrolled to achieve the planned enrollment. The sample size will also include former CVT-301-003 subjects who enrolled under previous versions of this protocol, but were no longer eligible under V4.0.

12.2. Study Populations

All patients who are enrolled in CVT-301-004E and receive at least 1 dose of CVT-301 will be included in the safety analyses and will be grouped according to the highest dose received. All patients who are enrolled in CVT-301-004E and who receive at least 1 dose of CVT-301 will be included in the efficacy analyses as well but will be grouped according to the randomized treatment.

12.3. Definition of Baseline

For all statistical analyses, except for assessments of withdrawal symptoms, the visit at which the CVT-301 treatment is initiated will be used as the baseline. This will be TV1 from the CVT-301-

004 study for actively treated patients, i.e. randomized to DL1 or DL2. However, TV1 of the CVT-301-004E study will be used as the baseline for all placebo-treated subjects from study CVT-301-004, for patients from study CVT-301-009, and for patients from the observational arm of study CVT-301-005 and other CVT-301 naïve patients.

12.4. Background and Demographic Characteristics

Demographics and baseline characteristics will be summarized descriptively for the safety/ITT population. 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 each dose level. For the patients who received CVT-301 treatment in the CVT-301-004 study, the total exposure will be the sum of exposure in the CVT-301-004 study and the CVT-301-004E study.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The TEAEs (i.e., events which start or worsen during the study treatment) will be tabulated by treatment group, system organ class, and preferred term. Both patient and event counts will be calculated. In addition, the TEAEs will be evaluated by seriousness, severity, and causality to the study treatment. The AEs leading to a premature discontinuation or dose adjustment will also be summarized. The AEs will be summarized by dose level (CVT-301 DL1 or CVT-301 DL2). Descriptive statistics will be used to describe the overall incidence of TEAE normalized for duration of exposure (number of TEAEs divided by the total exposure to CVT-301 measured as patient years). Furthermore, the time of onset of the TEAEs will be summarized.

For vital signs, ECG parameters, spirometry, the changes from pre-dose to post-dose assessments of the corresponding day will be calculated and compared between the treatment groups using descriptive statistics. For spirometry and safety laboratory variables, the differences in pre-dose values between study days will be described. Furthermore, the changes in the spirometry values and difference between the groups (DL1/DL2 or patients treated with CVT-301/placebo in CVT-301-004) will be estimated using a Mixed Model for Repeated Measurements (MMRM) similar to the one used for the efficacy variables. The proportions of patients meeting ATS quality criteria (and also for those 'rejected') will be summarized. Changes from baseline to follow-up in the rating scales for assessing suicidality, somnolence, and impulse control disorders will be summarized descriptively.

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.
- For the AWQ, DDS-PC, PHQ-9, Epworth Sleepiness Scale, C-SSRS, and UPDRS Parts 1 and 2, the change from baseline to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 of the withdrawal symptom assessment period will be summarized descriptively.

12.5.1. Interim Safety Data Review

Safety data will be reviewed by an independent 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, 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.

There will be no prospective interim evaluation of efficacy endpoint data.

12.6. Efficacy Analysis

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

All patients who are enrolled in CVT-301-004E and who receive at least 1 dose of CVT-301 will be included in the efficacy analyses as well but will be grouped according to the randomized treatment.

The data for patients who were enrolled in the CVT-301-004 study, the CVT-301-009 study and for the CVT-301-naïve patients study will be primarily analyzed together, while the patients who were enrolled in the CVT-301-003 study will be analyzed separately. A sensitivity analysis will be performed for the patients who enrolled in the CVT-301-004 study separately and for the CVT-301-naïve patients separately.

The changes within each dose level and the overall change from baseline in continuous efficacy variables will be estimated using an MMRM. Although the focus of this study is to describe the within-group changes, the differences between the dose levels will be estimated as well, but no inferential analyses regarding the between-group differences will be done. The model will include the treatment group (CVT-301 DL1 or CVT-301 DL2), visit, the stratification variables (Hoehn and Yahr disease severity scale rating and screening FEV1 and/or FEV1/FVC) and the interaction between the treatment group and visit as fixed factors. The baseline value will be used as a covariate, if available. The categorical data will be primarily evaluated descriptively. Each visit will be tested separately.

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 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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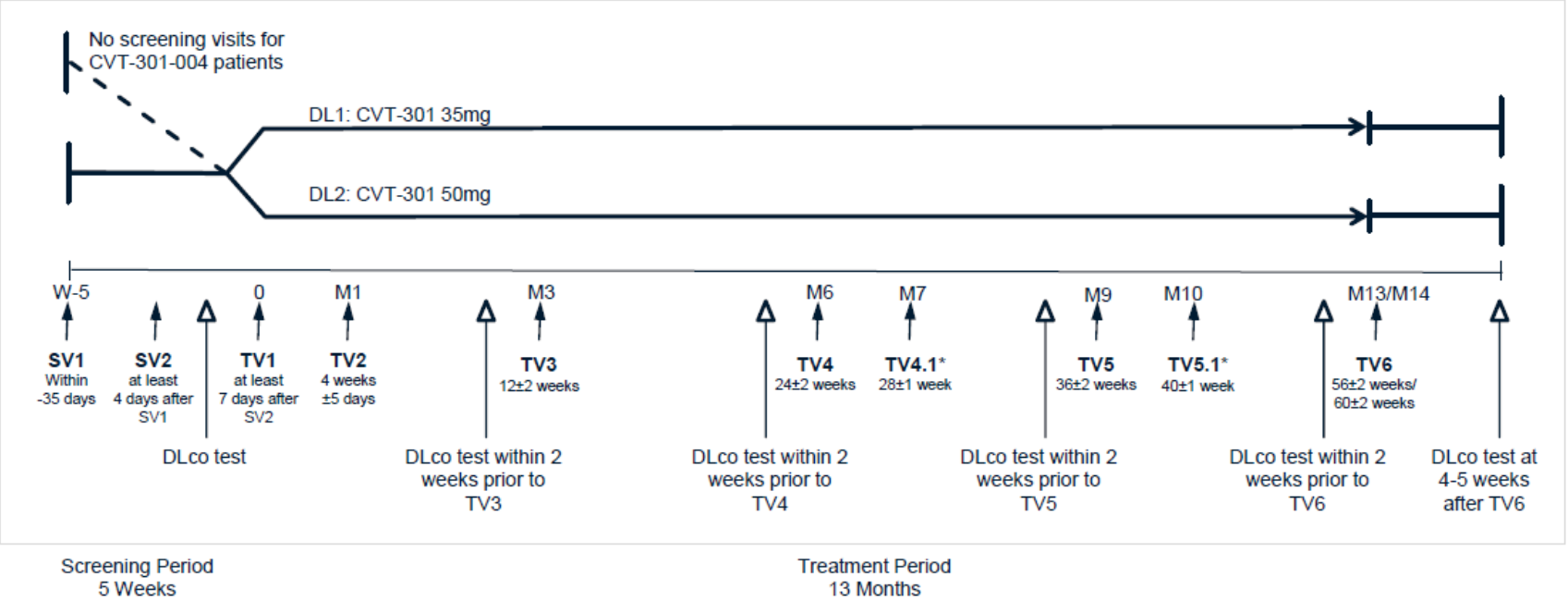
15. APPENDICES – TABLE OF CONTENTS

Appendix 1: Overall Visit Schedule Schematic



Abbreviations: DL1 = Dose Level 1; DL2 = Dose Level 2; DLco = carbon monoxide diffusing capacity; M = month; SV = screening visit; TV = treatment visit; W = weeks.

*TV4.1 for patients who enter the study drug holiday after TV4; TV5.1 for patients who enter the study drug holiday after TV5.

Appendix 2: Time and Events Table-Screening Visit 1 (SV1) for CVT-301-Naïve Patients (including CVT-301-005 observational arm patients) and CVT-301-009 Patients (within 35 days prior to randomization)

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 medication	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 Parts 1, 2 and 4		X			
UPDRS Part 3		X	X		
Patient training on self-report of ON/OFF states		X	X		
ON/OFF Concordance testing[3]		X	X		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[4]				
Inhaler training using sham capsules		X	X		

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**
Distribute PD Diary and Screening ON/OFF Episodes Log and review instructions for completion[5]				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]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.
[4]Document whether patient is fasting (≥4 hours after last snack or meal).
[5]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) for CVT-301-Naïve Patients (including CVT-301-005 observational arm patients) and CVT-301-009 Patients (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 PD medication dose/regimen	X				
Record any changes in concomitant medication	X				
Inhaler training using sham capsules and IFU[3]		X	X		
Patient training on assessment of ON/OFF state		X	X		
C-CSSR		X			
Epworth Sleepiness Scale		X			
QUIP		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 TV1)				X	
Post-SV2 telephone contact: call patient 4 to 6 days prior to TV1					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 Parts 1, 2, and 4		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 10.1.1.2 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 TV1.
[5]Document whether patient is fasting (≥4 hours after last snack or meal).

Appendix 4: Time and Events Table-Treatment Visit 1 (TV1) for CVT-301-004 Patients (1-14 days after TV4 in the CVT-301-004 study)

Procedures[1]	Arrival	Pre-dose	Time 0 (Dosing)[2]	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
Record usual PD medications	X									
Record time of patient's prior usual PD medication dose	X									
Concomitant medication	X									
Physical examination (full)	X									
ECG	X[3]									
Standard and orthostatic BP and HR	X[3]					X		X		
Respiratory rate	X[3]			X		X	X	X		
Spirometry	X[4]	X			X		X	X		
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[5]									
C-SSRS	X[4]									
Epworth Sleepiness Scale	X[4]									
UPDRS Parts 1 and 2	X[4]									
PHQ-9 (in ON state)	X									
AWQ and DDS-PC (in ON state)	X									
Impact of Parkinson's OFF Episodes Patient Survey[4]	X									
Review inhaler training	X									

Procedures[1]	**Arrival**	**Pre-dose**	**Time 0 (Dosing)**[2]	**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**
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion[6]	X									
Distribute study drug kits	X									
Self-administration of study drug (in OFF state)			X[2]							
Monitor for AEs	X									
Schedule next visit									X	
Post-TV1 telephone contact: call patient 1-3 days after TV1										X
Post-TV1 telephone contact: call patient 1 week prior to TV2										X

[1]Informed consent must be signed prior to performing any study procedures. Informed consent should have been signed at TV4 of the CVT-301-004 study.
[2]First dose of study medication preferably occurs between 2 and 5 hours after patient has taken normal morning dose of PD medication and after all pre-dose assessments are complete.
[3]Procedures can be done at any point after arrival and 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-Treatment Visit 1 (TV1) for CVT-301-Naïve Patients (including CVT-301-005 observational arm patients) and CVT-301-009 Patients (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									
Record time of patient's prior usual PD medication dose	X									
Record any changes in usual PD medication dose/regimen	X									
Concomitant medication	X									
PDQ-39 (in ON state)	X									
PHQ-9 (in ON state)	X									
AWQ and DDS-PC (in ON state)	X									
Physical examination (brief)	X									
UPDRS Parts 1 and 2 (preferably in ON state)	X									
S&E ADL (preferably in ON state)	X									
UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)	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			X		X	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
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[3,5]									
C-SSRS	X[3,4]									
Epworth Sleepiness Scale	X[3,4]									
QUIP	X[3,4]									
Impact of Parkinson's OFF Episodes Patient Survey	X[3,4]									
Review inhaler training	X									
Distribute PD Diary and Inhaled Dosing Log and review instructions for completion[6]	X									
Distribute study drug kits	X									
Self-administration of study drug (in OFF state)			X[1]							
Monitor for AEs	X									
Schedule next visit									X	
Post-TV1 telephone contact: call patient 1-3 days after TV1										X
Post-TV1 telephone contact: call patient 1 week before TV2										X

[1]First dose of study medication preferably occurs 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.
[3]Procedures can be done at any point after arrival and 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 6: Time and Events Table-Treatment Visit 2 (TV2) for all Patients (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 medication	X								
PDQ-39 (in ON state)	X								
PHQ-9 (in ON state)	X								
PGI-C (in ON state)	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) (preferably in ON state)	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[3]								
Electrocardiogram	X								
C-SSRS (preferably in ON state)	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 TV2	Post-TV2 Telephone Contact
Epworth Sleepiness Scale (preferably in ON state)	X								
QUIP (preferably in ON state)	X								
Impact of Parkinson's OFF Episodes Patient Survey (preferably in ON state)	X								
Distribute study drug kits	X								
Review inhaler training	X								
Distribute PD Diary and Inhaled Dosing Log; review instructions for completion[4]	X								
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule DLco and spirometry assessments[2] and next visit								X	
Post-TV2 telephone contact: call patient 1 week before TV3									X

[1]Dosing of study medication preferably occurs 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 and spirometry are to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
[3]Assessment can be done at any point after arrival and 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.

Appendix 7: Time and Events Table-Treatment Visit 3 (TV3) for all Patients (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								
Pre-TV3 DLco and spirometry assessments[2] (within 2 weeks prior to TV3/confirm complete and if not complete, re-schedule study visit	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 medication	X								
PDQ-39 (in ON state)	X								
PHQ-9 (in ON state)	X								
PGI-C (in ON state)	X								
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) (preferably in ON state)	X								
C-SSRS (preferably in ON state)	X								
Epworth Sleepiness Scale (preferably in ON state)	X								
QUIP (preferably in ON state)	X								
Impact of Parkinson's OFF Episodes Patient Survey (preferably in ON state)	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
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[4]								
Electrocardiogram	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[5]								
Distribute study drug kits	X								
Review inhaler training (if needed)	X								
Distribute PD Diary and Inhaled Dosing Log; review instructions for completion[6]	X								
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule DLco and spirometry assessments[2] and next visit								X	
Post-TV3 telephone contact: call patient 1 week before TV4									X

[1]Dosing of study medication preferably occurs 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 and spirometry are to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
[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 and 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 TV4; the Inhaled Dosing Log is to be completed daily through TV6.

Appendix 8: Time and Events Table-Treatment Visit 4 (TV4) for all Patients (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								
Pre-TV4 DLco and spirometry assessments[2] (within 2 weeks prior to TV4)/confirm complete and if not complete, re-schedule study visit	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 medication	X								
AWQ and DDS-PC (in ON state)	X[3]								
PDQ-39 (in ON state)	X								
PHQ-9 (in ON state)	X[3]								
PGI-C (in ON state)	X								
UPDRS Part 1 (preferably in ON state)	X[3]								
UPDRS Part 2 (preferably in ON state)	X[3,4]								
S&E ADL (preferably in ON state)	X[4]								
UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)	X								
C-SSRS (preferably in ON state)	X[3]								
Epworth Sleepiness Scale (preferably in ON state)	X[3]								
QUIP (preferably in ON state)	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 TV4	Post-TV4 Telephone Contact
Impact of Parkinson's OFF Episodes Patient Survey (preferably in ON state)	X								
Physical examination (full)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[5]								
Electrocardiogram	X								
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[6]								
Distribute study drug kits for patients not entering the study drug holiday	X								
Review inhaler training (if needed) for patients not entering the study drug holiday	X								
Distribute PD Diary and Inhaled Dosing Log; review instructions for completion[7]	X								
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule DLco and spirometry assessments [2] and next visit								X	
Post-TV4 telephone contact: call patient 1 week before TV5									X
For patients entering study drug holiday, schedule TV4.1[8]								X	
For patients entering study drug holiday, post-TV4 telephone contact[9]									X

[1]Dosing of study medication preferably occurs 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 and spirometry are to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.

[3]For patients who enter the study drug holiday at this visit. Also dispense copies to be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4. Complete in ON state after intake of first scheduled dose of standard oral PD medication. The self-report version of the C-SSRS and self-administered MDS-UPDRS Parts 1B and 2 will be dispensed for completion at home.
[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 and before dosing.
[6]Document whether patient is fasting (≥4 hours after last snack or meal).
[7]The PD Diary is to be completed for the 3 consecutive days prior to TV5; the Inhaled Dosing Log is to be completed daily through TV6, except during the study drug holiday.
[8]If applicable, study drug re-supply visit to be scheduled 28 days (+1 week) after TV4.
[9]If applicable, site staff will call the patient at 14 (±3) days after TV4 to remind them to complete the withdrawal questionnaires, and to inquire about potential adverse events and changes in concomitant medications.

Appendix 9: Time and Events Table-Treatment Visit 5 (TV5) for all Patients (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								
Pre-TV5 DLco and spirometry assessments[2] (within 2 weeks prior to TV5)/confirm complete and if not complete, re-schedule study visit	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 medication	X								
AWQ and DDS-PC (in ON state)	X[3]								
PDQ-39 (in ON state)	X								
PHQ-9 (in ON state)	X[3]								
PGI-C (in ON state)	X								
UPDRS Part 1 (preferably in ON state)	X[3]								
UPDRS Part 2 (preferably in ON state)	X[3,4]								
S&E ADL(preferably in ON state)	X								
UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)	X								
Physical examination (brief)	X								
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	X[4]								
Electrocardiogram	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 TV5	Post-TV5 Telephone Contact
Clinical laboratory tests (serum pregnancy test, if applicable)	X[5]								
C-SSRS (preferably in ON state)	X[3]								
Epworth Sleepiness Scale (preferably in ON state)	X[3]								
QUIP (preferably in ON state)	X								
Impact of Parkinson's OFF Episodes Patient Survey (preferably in ON state)	X								
Distribute study drug kits for patients not entering the study drug holiday	X								
Review inhaler training (if needed) for patients not entering the study drug holiday	X								
Distribute PD Diary and Inhaled Dosing Log; review instructions for completion[6]	X								
Self-administration of study drug (in OFF state)			X[1]						
Monitor for dyskinesia and ON/OFF states				X					
Monitor for AEs	X								
Schedule DLco and spirometry assessments[2] and next visit								X	
Post-TV5 telephone contact: call patient 1 week before TV6									X
For patients entering study drug holiday, schedule TV5.1[7]								X	
For patients entering study drug holiday, post-TV5 telephone contact[8]									X
Schedule an Unscheduled Visit, if applicable[9]									X

[1]Dosing of study medication preferably occurs 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 and spirometry are to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
[3]For patients who begin the study drug holiday at the end of this visit. Also dispense copies to be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV5. Complete in ON state after intake of first scheduled dose of standard oral PD medication. The self-report version of the C-SSRS and self-administered MDS-UPDRS Parts 1B and 2 will be dispensed for completion at home.
[4]Assessment can be done at any point after arrival and 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 TV6; the Inhaled Dosing Log is to be completed daily through TV6, except during the study drug holiday
[7]If applicable, study drug re-supply visit to be scheduled 28 days (+1 week) after TV5.
[8]If applicable, site staff will call the patient at 14 (±3) days after TV5 to remind them to complete the withdrawal questionnaires, and to inquire about potential adverse events and changes in concomitant medications.
[9]Patients who have already completed TV5 at the time of implementation of protocol Version 5.2 will have the option to consent to this amendment at an Unscheduled Visit prior to TV6, at which time they will receive an additional 4 weeks of study drug.

Appendix 10: Time and Events Table-Treatment Visit (TV6) for all Patients (13 Months [56±2 Weeks or 14 Months [60 ±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	Post-TV6 DLco/spirometry Assessment
Collect, review, sign and date PD Diary and Inhaled Dosing Log	X							
Collect empty capsules, inhalers, and unused supplies	X							
Pre-TV6 DLco and spirometry assessments[2] (within 2 weeks prior to TV6)/confirm complete (and if not re-schedule study visit)[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 medication	X							
AWQ and DDS-PC (in ON state)	X[4]							
PDQ-39 (in ON state)	X							
PHQ-9 (in ON state)	X[4]							
PGI-C (in ON state)	X							
UPDRS Part 1 (preferably in ON state)	X[4]							
UPDRS Part 2 (preferably in ON state)	X[4,5]							
S&E ADL (preferably in ON state)	X[5]							
UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)	X							
Physical examination (brief)	X							
Vital signs (standard BP, HR, and RR and orthostatic BP and HR)	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	Post-TV6 DLco/spirometry Assessment
Electrocardiogram	X							
C-SSRS (preferably in ON state)	X[4]							
Epworth Sleepiness Scale (preferably in ON state)	X[4]							
QUIP (preferably in ON state)	X							
Impact of Parkinson's OFF Episodes Patient Survey (preferably in ON state)	X							
Clinical laboratory tests (including serum pregnancy test, if applicable)	X[7]							
Self-administration of study drug (in OFF state)			X[1]					
Monitor for dyskinesia and ON/OFF states				X				
Monitor for AEs	X							
Post-TV6 DLco and spirometry assessments[2] (at 4-5 weeks after TV6/Early Termination Visit)[3]								X
For patients entering the withdrawal sub-study, post-TV6 Telephone contact[8]								

[1]Dosing of study medication preferably occurs 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 and spirometry are to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
[3]Patients who withdraw early will undergo all of the TV6 assessments (except the pre-TV6 DLco and spirometry assessment) at the time of withdrawal. They will be scheduled to undergo the post-TV6 DLco and spirometry assessments 4-5 weeks following completion of the Early Withdrawal Visit.
[4] For patients who begin the study drug holiday at the end of this visit. Also dispense copies to be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. Complete in ON state after intake of first scheduled dose of standard oral PD medication. The self-report version of the C-SSRS and self-administered MDS-UPDRS Parts 1B and 2 will be dispensed for the post TV6 time points.
[5]Preferably in the ON state, but these must be performed before any other study evaluation.
[6]Assessment can be done at any point after arrival and before dosing.
[7]Document whether patient is fasting (≥4 hours after last snack or meal).
[8]If applicable, site staff will call the patient at 14 (±3) days and 28 (±3) days after TV6/Early Withdrawal to remind them to complete and return the withdrawal questionnaires, and to inquire about potential adverse events and changes in concomitant medications.

Appendix 11: Time and Events Table-Treatment Visit (TV) 4.1 and TV5.1 for all Patients (28 days+1 week] after TV4 or TV5)*

Procedures	
Collect completed questionnaires	X
Record any changes in usual PD medication dose/regimen	X
Record any changes in other concomitant medications	X
Record any adverse events	X
Distribute study drug kits	X
Review inhaler training (if needed)	X
Distribute PD Diary and Inhaled Dosing Log; review instructions for completion (if not done at prior visit)	X

*To occur 28 days (+1 week) after TV4 or TV5 (depending on when the patient begins the study drug holiday)

Appendix 12: 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 13: 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) for CVT-301-naïve patients and CVT-301-009 patients, and at TV1, TV3, TV4, TV5, and TV6, if applicable; magnesium; C-Reactive Protein

Appendix 14: 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 15: 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 16: 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 17: 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

Appendix 18: Spirometry Alert and Review Process Diagram