CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson’s Disease Patients With Motor Response Fluctuations (OFF Phenomena) (SPAN-PD™)

Protocol Number: CVT-301-004

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Development Phase: Phase 3

Study Sponsor: Civitas Therapeutics, Inc.
190 Everett Ave
Chelsea, MA 02150
USA

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-CONFIDENTIAL-

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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

<table>
<thead>
<tr>
<th>Role</th>
<th>Contact Information</th>
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| Sponsor                                   | Civitas Therapeutics, Inc.  
190 Everett Ave  
Chelsea, MA 02150  
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<p>| Sponsor’s Responsible Medical Director    |                                                          |
| CRO Global Study Manager                  |                                                          |
| CRO Medical Monitor                       |                                                          |
| CRO Safety (Pharmacovigilance) Reporting  |                                                          |
| Clinical Laboratory                       |                                                          |
| Spirometry and ECG Central Laboratory     |                                                          |</p>
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### 2. SYNOPSIS

<table>
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<tr>
<th>Title of Study:</th>
<th>A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson’s Disease Patients With Motor Response Fluctuations (OFF Phenomena) (SPAN-PD™)</th>
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<td>Protocol Number:</td>
<td>CVT-301-004</td>
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<td>Investigators/Study Sites:</td>
<td>This study will be conducted at approximately 70 sites in the United States of America (USA), Canada, and Europe.</td>
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<td>Phase of Development:</td>
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#### Objectives:

**Primary Objective**

To compare the effects of CVT-301 versus placebo on the change from pre-dose in Unified Parkinson’s Disease Rating Scale (UPDRS) Part 3 motor score at 30 minutes following treatment of patients experiencing an OFF episode at Treatment Visit 4 (TV4) (Week 12). The comparisons related to the primary and secondary objectives will be carried out in a hierarchical manner, see statistical section below.

**Key Secondary Objectives**

The key secondary objectives evaluating the effect of CVT-301 versus placebo at TV4 will be evaluated in a hierarchical manner:

1. 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).

2. Change from pre-dose in UPDRS Part 3 motor score at 20 minutes following treatment of patients experiencing an OFF episode.

3. Proportion of patients who improved based on the Patient Global Impression of Change (PGI-C) rating scale measured pre-dose.

4. Change from pre-dose in UPDRS Part 3 motor score at 10 minutes following treatment of patients experiencing an OFF episode.

5. Change from baseline in total daily OFF time assessed by the patient and recorded in the PD Diary for 3 consecutive days prior to TV4.

First, the parameters defined in the primary and the key secondary objectives will be compared between CVT-301 Dose Level 2 (DL2; high dose) and placebo in the order defined above. This is followed by the comparison of the parameters, as defined in primary and the key secondary objectives between CVT-301 Dose Level 1 (DL1; low dose) and placebo in the order defined above.
### Additional Secondary Objectives

The following are additional secondary objectives evaluating the effect of CVT-301 versus placebo at TV4:

- Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively for CVT-301 DL2, CVT-301 DL1 and placebo.
- Change from pre-dose in UPDRS Part 3 motor score at 60 minutes following treatment of patients experiencing an OFF episode.
- Change from pre-dose in UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode.
- Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11-point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes.
- Change from baseline in total daily ON time without dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia, assessed by the patient and recorded in the PD Diary.
- Change from baseline visit UPDRS Part 2 score.
- Change from baseline visit Schwab and England (S&E) Activities of Daily Living (ADL).
- Change from baseline visit 39-Item Parkinson’s Disease Questionnaire (PDQ-39).
- Change from baseline visit 9-Item Patient Health Questionnaire (PHQ-9).
- Change from baseline visit Impact of Parkinson’s OFF Episodes Patient Survey

The additional secondary objectives will be tested independently for both dose groups vs placebo.

### Safety Objectives:

- To characterize the effects of CVT-301 on safety and tolerability, assessed by adverse event (AE) reports, physical examination, vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), spirometry (forced expiratory volume in 1 second [FEV1] and FEV1/forced vital capacity [FVC] ratio), the Parkinson’s Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Change from baseline visit UPDRS Part 4 measures of motor fluctuations (dyskinesias [Questions 32-35] and wearing off
- Occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic.
- To evaluate the ability of Parkinson’s disease (PD) patients to perform American Thoracic Society (ATS) quality carbon monoxide diffusion capacity (DLco) maneuver.
- To characterize the effect of CVT-301 on DLco.

Safety parameters will be determined at all treatment visits as well as at the follow up visit.

**Exploratory objectives:**
The outcome variables, as listed in the primary and secondary objectives, will also be measured at Treatment Visit 2 (TV2) and Treatment Visit 3 (TV3) in an exploratory manner, as applicable.

### Study Design:

Patients enrolled in the study in the prior version of the protocol should continue under the prior version and new patients enrolled in the study under this amendment should continue under this amendment.

This study is a randomized, double-blind, placebo-controlled, multicenter study of inhaled CVT-301 or placebo for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes). Approximately 345 patients will be randomized in a 1:1:1 ratio to receive inhaled CVT-301 DL1 (target nominal respirable dose of 35 mg levodopa [LD] fine particle dose [FPD]), CVT-301 DL2 (target nominal respirable dose of 50 mg LD FPD), or placebo; randomization will be differentiated by the patient’s Hoehn and Yahr disease severity scale rating (<2.5 versus ≥2.5) to balance the severity of disease in each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥ 60% of predicted and FEV1/FVC ratio ≥ 70%).

Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode to deliver the intended dose). The capsules for DL1, DL2, and placebo will appear identical in order to maintain blinding. The first dose of blinded inhaled study drug will be given in the clinic at TV1, at which only safety evaluations will be performed post-dose.

The study has 3 periods: a screening period, treatment period, and follow-up period. There are a total of 6 or 7 planned visits (2 screening visits, 4 treatment visits, and 1 follow-up visit [for patients who do not continue into the extension study, CVT-301-004E, or for those who terminate the study early]). For each patient, the planned treatment period will be approximately 12 weeks, and maximum anticipated study duration, including screening and follow-up, will be approximately 19 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, 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 to the original randomized dose level (i.e., 2 capsules). This return to randomized dose must take place at the in-clinic visit only and may only be done once during the study. 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 not be eligible for any additional up-titration to the original dose. Spirometry will be assessed at the neurology sites for screening and TV1. The baseline spirometry and DLco assessments 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. Clinical relevance of observed changes will be determined immediately by trained pulmonologists. 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

The screening period, which will take place within 35 days prior to randomization, will include 2 separate visits. Screening Visit 1 (SV1) and Screening Visit 2 (SV2) must be separated by at least 4 days. The screening period may be extended further upon Sponsor approval if repeat screening assessments are required.

#### Screening Visit 1 (SV1) (up to 35 days prior to TV1)

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). Patient’s PD medications, including standard LD-containing regimen...
(number of times per day that LD-containing medications are administered and total daily LD dose will be recorded) and any other concomitant medications will be recorded and reviewed to ensure that specified 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; completion of the Pulmonary Function Baseline Questionnaire; ECG; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); spirometry for determination of FEV1, FVC, and the FEV1/FVC ratio (while the patient is in an ON state). Patients will undergo UPDRS Part 1, 2, 3 and 4 assessments while in an ON state and training on self-recognition of ON and OFF states and rating assessments preferably 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 of both ON and OFF states and must be at least 75% concordant 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 at least 75% concordance by the end of SV2, they will be considered screening 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 the ON state.

Patients will remain in the clinic and further PD medications will be withheld until they turn into an OFF state. The spirometry evaluation, UPDRS Part 3 assessment, patient training on self-report of ON/OFF states, and inhaler training should be repeated when the patient is 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 document the discrete number of OFF episodes experienced by the patient 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 diaries/data collection tools. Patients will be monitored for AEs throughout the visit.

Clinic staff will arrange to speak with patients by telephone ~4 days prior to SV2 to confirm the next study visit and to remind patients of the study procedures required prior to the next scheduled study visit (including completion of the PD Diary and Screening ON/OFF Episodes Log).

Screening Visit 2 (SV2) (at least 4 days after SV1)

For the 3 consecutive days prior to SV2, patients will complete the PD Diary and the Screening ON/OFF Episodes Log. Before arrival at the clinic for SV2, the patient will take all of their usual prescribed non-PD medications and PD medications, including LD-containing PD medications.

At the clinic, the clinic staff will review the PD Diary and Screening ON/OFF Episodes Log to determine that patients are able to perform these procedures correctly and to determine eligibility. The staff will confirm that the usual PD medication dose has not changed. Concomitant medications will be recorded. Patients will be trained again on the proper inhalation 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. 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 (should be assessed in the ON state), physical examination, ECG, standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR), spirometry (assessed in both the ON and OFF states), UPDRS Part 3 (assessed in both the ON and OFF states), UPDRS Part 1, 2 and 4, ON/OFF concordance testing (assessed in both the 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 eligibility determination and randomization. Any repeat assessments should be performed in the respective motor state as described for SV1.

Before patients return to the clinic for TV1 (baseline visit), they will be randomized to receive CVT-301 DL1, CVT-301 DL2, or placebo in a 1:1:1 randomization scheme. Patients will not be randomized until the clinic staff has received confirmation of eligibility from the external eligibility reviewer (subjects requiring pulmonary adjudication may not be randomized until completion of pulmonologist review). Sites must allow 5 business days between time of randomization and TV1 to allow time for drug to be shipped and received. 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 treatment groups and by screening FEV1 and/or FEV1/FVC, as described previously (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥ 60% of predicted and FEV1/FVC ratio ≥ 70%).

The clinic staff will schedule patients to undergo DLco and spirometry assessments at the pulmonary function lab. These assessments will 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 DLco and spirometry visit, a slow vital capacity maneuver will be performed, followed by DLco, and then spirometry.

All patients, regardless of treatment assignment, will continue with their usual prescribed standard PD medication regimen for the study duration. This regimen should not be changed for the duration of this study.

Clinic staff will arrange to speak with patients by telephone 4 to 6 days prior to TV1 to confirm the DLco and spirometry visit 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 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 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.

**Treatment Period**

**Treatment Visit 1 (TV1) (Baseline; 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.
for baseline assessments (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.

At this visit, the following assessments should be performed:
- collection and review of the PD Diary and the Screening ON/OFF Episodes Log (the staff will document whether these were completed correctly, and sign and date each); confirmation that the DLco assessment has been performed (and if not, re-schedule the study visit);
- recording of time of patient’s prior usual PD medication dose; confirmation that the usual PD medication dose/regimen has not changed;
- recording of all concomitant treatments. Patients will undergo a brief physical examination, standard vital sign assessments (BP, HR, and RR), orthostatic vital sign assessments (BP and HR), and ECG.

In addition the following assessments will be recorded:
- PDQ-39 and the Patient Health Questionnaire-9 (PHQ-9), both 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).

Patients will also undergo spirometry evaluations (preferably performed in an ON state) and clinical laboratory tests (with documentation of fasting status) including pregnancy test, if applicable. Patients will be re-trained on the proper use of the inhaler using sham capsules (per the IFU), including a specific review of the IFU.

The patients will be given 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, and TV4).
2) **Inhaled Dosing Log**: for recording the number of times the inhaler was used and the number of capsules used for each inhalation treatment (to be completed daily throughout the 12-week treatment period).

Study drug kits will be distributed; 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.

Under clinic staff supervision, preferably between 2 and 5 hours after receiving their previous dose of oral PD medications (in the OFF state), patients will prepare and self-administer their first dose of blinded study drug (i.e., 2 capsule inhalations of either CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

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 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 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).

Clinic staff will arrange to speak with patients by telephone 1 to 3 days after TV1 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 4 to 6 days before each visit for TV2, TV3, and TV4 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 has taken place (prior to TV3 and TV4), to confirm the next study 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).
At-Home Dosing

At TV1, TV2, and TV3, patients will receive study drug kits and the IFU to take home with them. Patients will be instructed to take their standard oral PD medications as prescribed on their usual schedule of administration, which will not be modified during the 12 weeks of study drug treatment.

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.

In the event that an OFF state is not sufficiently resolved within 45 minutes of completing the last capsule inhalation, patients should 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. Also, they may not add any new PD medications during the study nor alter their usual PD medication dose or dose regimen during the study.

Patients will complete the PD Diary for the 3 consecutive days prior to TV2, TV3, and TV4. Patients will complete the Inhaled Dosing Log every day during the 12-week treatment period. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV1 and 4 to 6 days prior to each visit for TV2, TV3, and TV4.

Treatment Visit 2 (TV2) (Week 4; 28±5 days after TV1)

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. 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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD
Clinic staff will collect, review, sign, and date the PD Diary and Inhaled Dosing Log, record the time that patients took their usual PD medications prior to the visit, and confirm that there were no changes in the usual PD medication dose/regimen. The staff will collect the empty capsules, inhalers, and unused supplies. The staff will record any changes in concomitant medications. Patients will undergo a brief physical examination, standard vital sign assessments (BP, HR, and RR) and orthostatic vital sign assessments (BP and HR).

In the OFF state, the patient will undergo UPDRS Part 3 assessments immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

Efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. The PD Diary and Inhaled Dosing Log will be provided to patients, and the instructions for completion will be reviewed. 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. Patients will be monitored 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 the treatment of additional OFF episodes).

Clinic staff will also schedule a DLco and spirometry assessment to occur at the pulmonary function facility at 14±3 days after TV2. 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.

Clinic staff will arrange to speak with patients by telephone 4 to 6 days before 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 (14±3 days after TV2), to confirm their next study visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log).

**Treatment Visit 3 (TV3) (Week 8; 56±5 days after TV1)**

Patients will record their use of inhaled study medication each day in the Inhaled Dosing Log and complete the PD Diary during the 3 consecutive days prior to TV3. 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.

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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

Clinic staff will confirm the DLco and spirometry visit was completed (and if not, re-schedule the study visit), collect, review, sign, and date the PD Diary and Inhaled Dosing Log, record the time that patients took their usual PD medications prior to the visit, and confirm that there were no changes in the usual PD medication dose/regimen. The staff will collect the empty capsules, inhalers, and any unused supplies. The staff will record any changes in concomitant medications. Patients will undergo a brief physical examination, standard vital sign assessments (BP, HR, and RR) and orthostatic vital sign assessments (BP and HR).

In addition the following assessments will be recorded: PDQ-39, PHQ-9 and PGI-C scale (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)

Clinic staff will provide study drug kits and review inhaler training with the patient (if needed).

The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will undergo UPDRS Part 3 assessments immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and
preferably between 2 and 5 hours after their prior oral PD medication. Efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose. The PD Diary and Inhaled Dosing Log will be provided to patients, and the instructions for completion will be reviewed. 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. Patients will be monitored 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 the treatment of additional OFF episodes).

Clinic staff will also schedule a DLco and spirometry visit for 7±3 days before TV4. Assessments that take place at the pulmonary function lab should be performed in an ON state (as reported by the patient to the pulmonary technician). 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 4 to 6 days before 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 (7±3 days before TV4), to confirm their next study visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log).

Treatment Visit 4 (TV4) (Week 12; 84±5 days after TV1)

Treatment Visit 4 will constitute the end-of-treatment visit. Patients will record their use of inhaled study medication each day up to TV4 in the Inhaled Dosing Log; in addition, they will complete the PD Diary during the 3 consecutive days prior to TV4. 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. 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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

Upon arrival, the following will be performed: confirmation that the
DLco and spirometry visit was completed (and if not, re-schedule the study visit); collection and review of patient PD Diary and Inhaled Dosing Log (each must be signed and dated); confirmation that there were no changes in the usual PD medication dose/regimen; recording of the time of the patient’s prior usual PD medication and dose; collection of empty capsules, inhalers, and any unused supplies; a review of concomitant medications. Patients will undergo a brief physical examination, standard vital sign assessments (BP, HR, and RR), orthostatic vital sign assessments (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).

Clinic staff will provide a new inhaler for study drug administration. Patients will use blinded study drug from the supplies brought to the visit.

The patient will remain in the clinic until he/she goes into the OFF state. In the OFF state, the patient will undergo UPDRS Part 3 assessments immediately pre-dose, following which the patient will prepare and then self-administer (under staff supervision) the entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

Efficacy responses will be assessed by recording: (1) UPDRS Part 3 evaluations at 10, 20, 30, and 60 minutes post-dose; (2) the occurrence and severity of dyskinesia; and (3) whether the patient converted to an ON state during the 60-minute post-dose time period and if so, whether he/she was still in an ON state at 60 minutes post-dose.

Patients will undergo clinical laboratory tests (with documentation of fasting status) including a serum pregnancy test, if applicable. Patients will be monitored for AEs throughout the visit. If the patient is in an OFF state 60 minutes after inhalation, patients will resume their standard oral dose of PD medication and be discharged from the clinic after adequate motor function resumes and all scheduled study procedures have been completed.

**Post-Treatment Evaluations and Procedures**

Patients who successfully complete the study through TV4 will be offered the opportunity to consent to a long-term (12-month) treatment extension study (CVT-301-004E) and study visits will be scheduled in accordance with that protocol. Eligibility for CVT-301-004E will be based, in part, on successful completion of study procedures, including the final DLco and spirometry visit at the pulmonary function lab.

**Follow-up Period**

Follow-up Visit (7-14 days after TV4, for patients *not* continuing in the CVT-301-004E study or for patients who terminate study early)
Patients who are not entering the long-term extension study, CVT-301-004E, will return for the Follow-up Visit 7-14 days after TV4. The patients will be questioned as to whether they are on a stable regimen of PD medications, and the following assessments will be performed: a review of concomitant medications; a recording of any AEs; a brief physical examination; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); ECG; clinical laboratory tests (with documentation of fasting status).

If a patient withdraws early from the study, the assessments for the Follow-up Visit will be performed. If the termination occurs prior to TV4, then the following are also required in addition to the assessments for the Follow-up Visit: collect, review, sign, and date the PD Diary and Inhaled Dosing Log; confirm that there were no changes in the usual PD medication dose/regimen; collect empty capsules, inhalers, and unused supplies;

In addition the following assessments will be recorded in the follow-up visit: UPDRS Part 4 (Questions 32-35 and 36-39); QUIP; Epworth Sleepiness Scale; and C-SSRS (preferably in the ON state).

If the early termination is after the start of treatment and more than 14 days following any post-treatment DLco and spirometry visit, a DLco and spirometry visit at the pulmonary function lab will be performed as close to the time of study withdrawal as possible.

**Selection of Patients:**

Male and female patients between the ages of 30 and 85 years are eligible for participation in this study if they meet all of the following inclusion criteria and do not meet any of the exclusion criteria.

**Inclusion Criteria:**

- Has signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form before any protocol-specific screening procedures are performed.
- Is a male or female aged 30 to 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
- Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the UK Brain Bank criteria, diagnosed after the age of 30 years.
- Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
- Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD...
<table>
<thead>
<tr>
<th>Diary (on 3 consecutive days) during the screening period.</th>
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<tr>
<td>- 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.</td>
</tr>
<tr>
<td>- 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.</td>
</tr>
<tr>
<td>- 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.</td>
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<tr>
<td>- Patients should be stable on other PD medications for at least 4 weeks prior to SV1.</td>
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<tr>
<td>- Patients must have a ≥ 25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.</td>
</tr>
<tr>
<td>- Patients must understand (with or without caregiver assistance) their daily medication regimen and must agree that they will not change their daily medication doses during the study.</td>
</tr>
<tr>
<td>- Patients must have normal cognition as confirmed by a score of ≥ 25 on the MMSE.</td>
</tr>
<tr>
<td>- 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 &gt; 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 &lt; 60% of predicted or an FEV1/FVC ratio that is &gt;60% to &lt;70% in order to determine eligibility. Patients with an FEV1/FVC ratio that is &gt;60% to &lt;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.)</td>
</tr>
</tbody>
</table>

Exclusion Criteria:

- Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures.
- Pregnant or lactating females or females wishing to become pregnant.
- Patients who have any known contraindication to the use of LD.
including a history of malignant melanoma or a history of narrow-angle glaucoma.

- Patients who have had previous surgery for PD (including but not limited to deep brain stimulation or cell transplantation) or plan to have stereotactic surgery during the study period.

- 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).

- 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 14 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 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.

- Patients who have participated in any prior CVT-301 study, regardless of treatment group assignment.

- 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: Approximately 345 patients will be randomized, so that at least approximately 258 patients will complete the study.

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. CVT-301 will be supplied in white opaque size 00 hypromellose (hydroxypropyl methylcellulose [HPMC]) capsules.

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.

The 2 selected CVT-301 dose levels are based on safety and pharmacokinetic (PK) data from Studies CVT-301-001 and CVT-301-006 in healthy adult volunteers, the safety, PK and pharmacodynamic data from Study CVT-301-002 in PD patients with motor fluctuations, and the safety and efficacy data from Study CVT-301-003 in PD patients with motor fluctuations.

In order to maintain the blind, all patients will be given identical-looking study drug kits and instructed to inhale 2 capsules (1 capsule for each inhalation) for each dose. Patients may sip water in between capsule inhalations, if needed.

Reference Therapy: Placebo Control
Placebo inhalation powder will be supplied in white opaque size 00 HPMC capsules, each at a nominal fill weight of 10 mg. Placebo inhalation powder is inhalation-grade lactose monohydrate, National Formulary (NF). The particle size and dose of the lactose was selected to provide comparable head deposition of inhalation powder and to mimic the sensation of inhalation. Placebo capsules will be delivered using CVT-301 inhalers. In order to maintain the blind, placebo patients will be instructed to take 2-capsule inhalations for each dose. The study drug kits will be identical in appearance to the active investigational therapy kits.

Treatment Duration: For each patient, the planned treatment period will be 12 weeks. Each patient will self-administer up to 5 doses of inhaled study drug per day for 12 weeks. The maximum anticipated study duration including screening (and follow-up if not enrolled in the extension study) will be approximately 19 weeks.

Criteria for Evaluation: Efficacy Criteria
Efficacy will be evaluated from both in-clinic and at-home (out-patient) assessments, as outlined by the following criteria:
Based on In-Clinic Evaluations:
- UPDRS Part 3 motor score, assessed pre-dose and at 10, 20, 30, and 60 minutes following treatment in the clinic. Occurrence of an ON state during the 60-minute post-dose period and if an ON state occurs during the 60-minute post-dose, whether or not the patient is still in the ON state at 60 minutes post-dose.
- 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.

**Safety Criteria**
Safety will be assessed from physical examinations, AE/SAE reports, standard and orthostatic vital signs (BP, HR, and RR), clinical laboratory values (hematology and biochemistry), ECGs, lung function (spirometry and DLco), the QUIP, Epworth Sleepiness Scale, and the C-SSRS. Additionally, safety will be assessed with:
- Occurrence and severity of examiner-rated dyskinesia following study medication administration in the clinic.
- UPDRS Part 4 Questions 32-35 and 36-39

**Statistical Methods and Planned Analyses:**
Randomized patients who receive at least 1 dose CVT-301 or placebo will be included in the safety and intent-to-treat (ITT) populations.

**Efficacy Analyses**
In the analysis of all efficacy endpoints, the patients in the ITT population will be grouped according to the randomized treatment group.

**Primary and Secondary Analyses**
The primary endpoint of the study is the change from pre-dose in the UPDRS Part 3 score at 30 minutes post-dose. The differences between CVT-301 DL1, CVT-301 DL2, and placebo at TV4 in the primary variable will be estimated using a Mixed Model for Repeated Measurements (MMRM) with contrasts. The model will include the treatment group (CVT-301 DL1, CVT-301 DL2, or placebo), visit (TV2, TV3, or TV4), the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) and the interaction.
between the treatment group and visit as fixed factors. The OFF-state baseline UPDRS part 3 score will be included as a covariate.

Outcome variables will be tested in a hierarchical order, as defined by the sequence of the primary and key secondary objectives, for DL2 first. If statistical significance is achieved for all parameters in the hierarchy for the DL2, the sequence will continue in the same order for DL1. The order of the testing is outlined below. The outcome parameter, which ranks first will be tested and the difference will be declared statistically significant if the nominal p-value is less than 0.05. Second, in case that the difference for the first objective is statistically significant, the objective ranked as second will be tested, and the difference will be declared statistically significant if the nominal p-value is less than 0.05. The testing will continue as long as the previously ranked objective was statistically significant.

The continuous secondary endpoints will be analyzed using MMRM model similar to the one used for the primary endpoint. For continuous variables which include pre-treatment baseline assessments, the baseline assessment will be included as a covariate in the model instead of the OFF-state baseline UPDRS part 3 score.

The categorical endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC). Each visit will be tested separately.

**Testing Hierarchy**

The outcome parameters, as specified in the primary and the secondary objectives, will be evaluated in the following order:

1. Primary objective: DL2 versus placebo
2. Secondary objective #1: DL2 versus placebo
3. Secondary objective #2: DL2 versus placebo
4. Secondary objective #3: DL2 versus placebo
5. Secondary objective #4: DL2 versus placebo
6. Secondary objective #5: DL2 versus placebo
7. Primary objective: DL1 versus placebo
8. Secondary objective #1: DL1 versus placebo
9. Secondary objective #2: DL1 versus placebo
10. Secondary objective #3: DL1 versus placebo
11. Secondary objective #4: DL1 versus placebo
12. Secondary objective #5: DL1 versus placebo

**Safety Analyses**

In the analysis of safety data, the patients in the safety population will be grouped according to the treatment received. Adverse events will be tabulated by treatment group according to the Medical Dictionary
Treatment-emergent adverse events (TEAEs) will be summarized by body system and preferred term. Descriptive statistics will be used to compare the overall incidence of TEAEs between patients receiving inhaled CVT-301 and inhaled placebo. For vital signs, ECG parameters, spirometry, and DLco, 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, DLco, and safety laboratory variables, the differences in pre-dose values between the study days will be compared. Changes from baseline to follow-up in the rating scales for assessing suicidality, somnolence, and impulse control disorders will be summarized descriptively. Demographics and baseline characteristics will be summarized descriptively.

**Sample Size**

The sample size of the study is based on the primary variable of the study: the change in the UPDRS Part 3 score at 30 minutes post-dose. The study has been powered to detect a difference of 5 points in the mean change in the average UPDRS Part 3 score, assuming a standard deviation of 10.0 points. To achieve a power of 90%, a total of 86 patients per group are required using a two-sided significance level of 0.05. To account for a drop-out rate of approximately 25%, 115 patients per group will be randomized. In the event that the withdrawal rate exceeds 25%, additional patients may be enrolled to ensure that at least 258 patients complete the study.
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<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the plasma concentration-time curve</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CD</td>
<td>carbidopa</td>
</tr>
<tr>
<td>CD/LD</td>
<td>carbidopa/levodopa</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximal plasma concentration</td>
</tr>
<tr>
<td>COMT</td>
<td>catechol-O-methyltransferase</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia-Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>DDI</td>
<td>dopamine decarboxylase inhibitor</td>
</tr>
<tr>
<td>DPPC</td>
<td>dipalmitoyl phosphatidylcholine</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DL1</td>
<td>Dose Level 1</td>
</tr>
<tr>
<td>DL2</td>
<td>Dose Level 2</td>
</tr>
<tr>
<td>DLco</td>
<td>carbon monoxide diffusing capacity</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FEV1</td>
<td>forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FPD</td>
<td>fine particle dose (i.e., pulmonary-delivered dose)</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>GCP</td>
<td>good clinical practice</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>hCG</td>
<td>human chorionic gonadotropin</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>HPMC</td>
<td>hydroxypropyl methylcellulose</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IFU</td>
<td>instructions for use</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
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<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
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<tr>
<td>LD</td>
<td>levodopa</td>
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<tr>
<td>LIP</td>
<td>levodopa inhalation powder (CVT-301)</td>
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<tr>
<td>MAO-B</td>
<td>monoamine oxidase-B</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters mercury</td>
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<tr>
<td>MMRM</td>
<td>Mixed Model for Repeated Measurements</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>NaCl</td>
<td>sodium chloride</td>
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<tr>
<td>NF</td>
<td>National Formulary</td>
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<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PDQ-39</td>
<td>39-Item Parkinson’s Disease Questionnaire</td>
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<td>PGI-C</td>
<td>Patient Global Impression of Change</td>
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<tr>
<td>PHQ-9</td>
<td>Patient Health Questionnaire</td>
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<td>PK</td>
<td>pharmacokinetic</td>
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<td>PRN</td>
<td>as needed</td>
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<tr>
<td>QTcB</td>
<td>QT interval corrected using Bazett’s formula</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected using Fridericia’s formula</td>
</tr>
<tr>
<td>QUIP</td>
<td>Parkinson’s Disease Impulsive-Compulsive Disorders Questionnaire</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>S&amp;E</td>
<td>Schwab and England</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SUSAR</td>
<td>suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>SV</td>
<td>Screening Visit</td>
</tr>
<tr>
<td>SV1</td>
<td>Screening Visit 1</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>SV2</td>
<td>Screening Visit 2</td>
</tr>
<tr>
<td>T0</td>
<td>time of completion of inhalation of the last capsule of inhaled study treatment administered</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>TV1</td>
<td>Treatment Visit 1</td>
</tr>
<tr>
<td>TV2</td>
<td>Treatment Visit 2</td>
</tr>
<tr>
<td>TV3</td>
<td>Treatment Visit 3</td>
</tr>
<tr>
<td>TV4</td>
<td>Treatment Visit 4</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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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).

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\textsubscript{max}) and less variable maximal plasma concentration (C\textsubscript{max}) compared to oral LD administration. These PK attributes translated to pharmacodynamic advantages in a nonclinical model of Parkinson’s disease (Bartus 2004).

Two Phase 1 and two Phase 2 studies have been conducted with CVT-301. In a Phase 1 study (CVT-301-001), 26 healthy adult subjects received CVT-301 in doses ranging from 10 to 50 mg LD fine particle dose (FPD) following CD pre-treatment. A second Phase 1 study (CVT-301-006) has also completed, where 12 healthy adult male subjects received CVT-301 in doses ranging from 50 to 105 mg LD FPD. In a single dose Phase 2a study (CVT-301-002), 24 patients with PD who experienced motor fluctuations received CVT-301 (25 and 50 mg LD FPD). In a Phase 2b study (CVT-301-003), 86 patients with PD who experienced motor fluctuations self-administered CVT-301 (approximately 35 and 50 mg LD FPD) over one month, up to 3 times daily, as needed, for the treatment of OFF episodes.

Single doses of CVT-301, up to a lung-delivered dose of 105 mg LD fine particle dose (FPD) and chronic treatment with doses up to 50 mg LD FPD given up to 3 times daily have been observed to be generally safe and well tolerated. Following single dose administration, LD C\textsubscript{max} and area under the plasma concentration-time curve (AUC) increase in a dose proportional manner over a range of doses of 10 mg LD FPD to 105 mg LD FPD.

Following CVT-301 inhalation, plasma LD levels increase rapidly, providing potentially therapeutic increments within 5 to 10 minutes post-dose and reaching peak concentrations at approximately 15 to 20 minutes post-dose. Based on PK results from both healthy volunteers and PD patients, CVT-301 35 mg LD FPD is expected to provide an incremental mean increase in plasma LD concentration of approximately 400 to 600 ng/mL; CVT-301 50 mg LD FPD is expected to provide increases of approximately 700 to 900 ng/mL.

In a Phase 2a single dose, cross-over study (CVT-301-002), study medication was administered to PD patients approximately 4-5 hours following their prior PD medication, in the OFF state. Safety, LD PK and pharmacodynamic responses were evaluated over a 3-hour post-treatment period. CVT-301 50 mg LD FPD provided sufficient motor function improvement, resulting in improvement in both subjective and objective motor responses (timed tapping and Unified Parkinson’s Disease Rating Scale [UPDRS] Part 3 motor score), and was demonstrated to be clinically effective. Timed tapping responses and UPDRS Part 3 motor score showed onset of action as early as the first time points tested, 5 to 15 minutes post-dose, respectively. In the context of that experimental study design, CVT-301 25 mg LD FPD was minimally effective; consistent numerically greater improvements in the magnitude of pharmacodynamic effects were apparent, although these were not statistically significant.
In a Phase 2b study (CVT-301-003), inhaled study medication was to be used as near as possible to the emergence of the patient’s OFF symptoms. Based on this treatment paradigm, CVT-301 doses of 35 mg and 50 mg LD FPD were evaluated. CVT-301, when self-administered by PD patients as needed to treat OFF episodes up to 3 times daily, was safe and efficacious. Moreover, patients demonstrated ease in handling the delivery system with a standard training module that was used for this study, in accordance with the instructions for use (IFU). Both dose levels were associated with clinically important and statistically significant improvement in UPDRS Part 3 motor responses, with onset of action observed at the first time point tested (10 minutes). When used up to 3 times daily, total daily OFF time was reduced which was most evidence at the 50 mg LD FPD. There was no increase in ON time with dyskinesia as measured by the PD home diary.

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. The PK, pharmacodynamic, and efficacy data from Phase 2 studies of CVT-301 in PD patients with motor fluctuation support the concept that administration of CVT-301 to patients taking an oral LD/dopamine decarboxylase inhibitor (DDI)-based regimen results in rapid augmentation of the systemic LD plasma concentration that is sufficient to improve motor responses in patients experiencing an OFF episode.

The more rapid LD absorption following inhaled CVT-301 administration is expected to translate to rapid alleviation of motor OFF symptoms in patients experiencing OFF episodes. This randomized, multicenter, placebo-controlled, double-blind study will evaluate the efficacy and safety of inhaled CVT-301 compared with placebo in PD patients experiencing motor response fluctuations (OFF phenomena) as an outpatient (i.e., at home) and in the clinic. Patients will be randomized to receive CVT-301 35 mg LD FPD, CVT-301 50 mg LD FPD, or placebo in a 1:1:1 randomization scheme; randomization will be differentiated by the patient’s Hoehn and Yahr stage (<2.5 versus ≥ 2.5) to balance the severity of disease in each 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%).

During the 12-week 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), 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 4 in-clinic visits (TV1, TV2, TV3, and TV4). In-clinic efficacy measures include serial assessments of UPDRS Part 3 motor score following treatment in the clinic, the occurrence and severity of dyskinesia following treatment in the clinic, the 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. Patient safety will be evaluated using adverse event (AE) reports, physical examination, vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms [ECGs], spirometry, carbon monoxide diffusing capacity (DLco) maneuver, UPDRS Part 4 score (Questions 32-35 and 36-39), the Parkinson’s Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS). In-clinic and at-home efficacy and safety measures will be compared between treatment groups.

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

In addition, in a Phase 2b study, 86 PD patients used CVT-301 in the OFF state on approximately 4480 occasions. Based on these studies, it was determined that patients with moderate to severe PD can successfully use the current inhaler and capsule product configuration in the OFF state to prepare and self-administer the product.

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) compared with the usual standard of care (placebo 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. An analysis of the pharmacodynamic effects of CVT-301 assessed in the Phase 2 study, CVT-301-002, provides evidence that CVT-301 50 mg LD FPD appeared to be a clinically effective dose that resulted in rapid improvement in both subjective and objective responses in a significant proportion of patients. These effects were observed at plasma LD exposures that were generally less than would be expected from a standard oral dose of LD (e.g. carbidopa/levodopa [CD/LD] 25 mg/100 mg). CVT-301 25 mg FPD was demonstrated to be minimally effective under these study conditions. In a second Phase 2 study, CVT-301-003, CVT-301 35 mg and 50 mg LD FPD improved objective and subjective motor responses, with dose ordered effects observed for some response variables.

The 2 selected CVT-301 dose levels (approximately 35 mg LD FPD and 50 mg LD FPD) are based on safety and PK data from Studies CVT-301-001 and CVT-301-006 in healthy adult volunteers, the safety, PK and pharmacodynamic data from Study CVT-301-002 in PD patients.
with motor fluctuations, and the safety and efficacy data from Study CVT-301-003 in PD patients with motor fluctuations.

**CVT-301 (Levodopa Inhalation Powder)**

Clinically, CVT-301 is intended for use as an adjunct to a PD patient’s standard oral LD/DDI combination-based regimen. As with oral LD administration, and as consistent with the PK findings in study CVT-301-002, circulating DDI plasma concentrations are expected to be adequate to effectively slow the biotransformation, prolong the circulating half-life, and increase availability of LD to central tissues. Owing to the rapid absorption half-life and short lag time, plasma LD concentration excursions are expected to be generally additive to any systemic concentration at the time of administration in the OFF state. As shown in Studies CVT-301-001, CVT-301-002, and CVT-301-006, plasma LD exposures (both C_{max} and AUC) increased dose proportionally from 10 mg to 105 mg FPD.
In Study CVT-301-002, the rapid LD absorption following inhaled CVT-301 50 mg LD FPD administration showed a temporal advantage compared to placebo and oral LD dosing with respect to the early time to improvement in subjective and objective motor response in patients experiencing defined OFF episodes.

Placebo Inhalation Powder

The use of a placebo-treated group is standard in most trials of new therapies in PD. The clinical development of any new treatment of motor fluctuations (OFF episodes) in patients with PD requires unbiased evaluation of both subjective and objective motor response-associated endpoints. It is well established that some of these endpoints are subject to learning effects as well as patient and examiner/rater bias, both of which may influence study outcome. Placebo responses for many motor response endpoints have been well-characterized (Goetz 2000, Goetz...
2002, Goetz 2008, Nutt 2000). Therefore, this study is employing an inhaled placebo that is intended to provide a sensation associated with dry powder inhalation in order to minimize patient- and rater-based biases on motor function-related as well as safety-related endpoints.

Currently, the only approved treatment to provide rapid relief of OFF episodes is injectable apomorphine which is utilized infrequently; there are no other effective noninvasive treatment alternatives available. Presently, patients frequently await their next scheduled dose or self-medicate with an unscheduled dose of oral LD, the effectiveness of which is known to be variable and complicated by potential dose failure or delay in effect. The use of placebo in the proposed study will not put patients at undue risk. Patient eligibility is based on the fact that they are already experiencing OFF episodes as a naturally occurring consequence of their disease. Patients will be permitted to use their standard medication in accordance with their current practice if they experience prolonged OFF states, as outlined in this protocol (see Section 9.4.2).
6. STUDY OBJECTIVES

Primary Objective
To compare the effects of CVT-301 versus placebo on the change from pre-dose in UPDRS Part 3 motor score at 30 minutes following treatment of patients experiencing an OFF episode at TV4 (Week 12). The comparisons related to the primary and secondary objectives will be carried out in a hierarchical manner, see below.

Key Secondary Objectives
The key secondary objectives evaluating the effect of CVT-301 versus placebo at TV4 will be evaluated in a hierarchical manner:

1. 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).
2. Change from pre-dose in UPDRS Part 3 motor score at 20 minutes following treatment of patients experiencing an OFF episode.
3. Proportion of patients who improved based on the PGI-C rating scale measured pre-dose.
4. Change from pre-dose in UPDRS Part 3 motor score at 10 minutes following treatment of patients experiencing an OFF episode.
5. Change from baseline in total daily OFF time assessed by the patient and recorded in the PD Diary for 3 consecutive days prior to TV4

First, the parameters defined in the primary and the key secondary objectives will be compared between CVT-301 DL2 and placebo in the order defined above. This is followed by the comparison of the primary and the key secondary objectives between CVT-301 DL1 and placebo in the order defined above.

Additional Secondary Objectives
The following are additional secondary objectives evaluating the effect of CVT-301 versus placebo at TV4:

- Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively for CVT-301 DL2, CVT-301 DL1 and placebo.
- Change from pre-dose in UPDRS Part 3 motor score at 60 minutes following treatment of patients experiencing an OFF episode.
- Change from pre-dose in UPDRS Part 3 motor score at 10 minutes following treatment of patients experiencing an OFF episode.
- Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11-point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes.
- Change from baseline in total daily ON time without dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia, assessed by the patient and recorded in the PD Diary.
• Change from baseline visit UPDRS Part 2 score.
• Change from baseline visit S&E ADL.
• Change from baseline visit PDQ-39.
• Change from baseline visit PHQ-9.
• Change from baseline visit Impact of Parkinson’s OFF Episodes Patient Survey

The additional secondary objectives will be tested independently for both dose groups vs placebo.

Safety Objectives:

• To characterize the effects of CVT-301 on safety and tolerability, assessed by AE reports, physical examination, vital signs (BP, HR, and RR), clinical laboratory tests, 12-lead ECGs, spirometry (FEV1 and FEV1/FVC ratio), the QUIP, the Epworth Sleepiness Scale, and the C-SSRS.

• Change from baseline visit 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.

• To evaluate the ability of PD patients to perform American Thoracic Society (ATS) quality DLco maneuver.

• To characterize the effect of CVT-301 on DLco.

Safety parameters will be determined at all treatment visits as well as at the follow up visit.

Exploratory objectives:

The outcome variables, as listed in the primary and secondary objectives, will also be measured at TV2 and TV3 in an exploratory manner, as applicable.

7. INVESTIGATIONAL PLAN

Patients enrolled in the study in the prior version of the protocol should continue under the prior version and new patients enrolled in the study under this amendment should continue under this amendment.

7.1. Description of Overall Study Design and Plan

This study is a randomized, double-blind, placebo-controlled, multicenter study of inhaled CVT-301 or placebo for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes). Approximately 345 patients will be randomized in a 1:1:1 ratio to receive inhaled CVT-301 DL1 (target nominal respirable dose of 35 mg LD FPD), CVT-301 DL2 (target nominal respirable dose of 50 mg LD FPD), or placebo; randomization will be differentiated by the patient’s Hoehn and Yahr disease severity scale rating (<2.5 versus ≥ 2.5) to balance the severity of disease in each group and by screening
spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥ 60% of predicted and FEV1/FVC ratio ≥ 70%).

Each treated episode will require 2-capsule inhalations (i.e., 2 capsules used in the inhaler per treated episode to deliver the intended dose). The capsules for DL1, DL2, and placebo will appear identical in order to maintain blinding. The first dose of blinded inhaled study drug will be given in the clinic at TV1, at which only safety evaluations will be performed post-dose.

The study has 3 periods: a screening period, treatment period, and follow-up period. There are a total of 6 or 7 planned visits (2 screening visits, 4 treatment visits, and 1 follow-up visit [for patients who do not continue into the extension study, CVT-301-004E, or for those who terminate the study early]). For each patient, the planned treatment period will be approximately 12 weeks, and the maximum anticipated study duration, including screening and follow-up, will be approximately 19 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, 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 to the original randomized dose level (i.e., 2 capsules). This return to randomized dose must take place at the in-clinic visit only and may only be done once during the study. 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 not be eligible for any additional up-titration to the original dose.

Spirometry will be assessed at the neurology sites for screening and TV1. The baseline spirometry and DLco assessments will be performed at dedicated pulmonary function labs prior to TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry and DLco after TV1. Clinical relevance of observed changes will be determined immediately by trained pulmonologists.

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.
All patients should continue with their usual prescribed standard PD medication regimen for the study duration. This regimen should not be changed for the duration of this study. Patients will not be permitted to take PRN oral PD medications to manage OFF episodes.

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 9 and in Section 10.1.

8. STUDY POPULATION

The study population for this study includes PD patients with motor fluctuations who meet the following inclusion criteria and do not meet any of the following exclusion criteria.

8.1. Inclusion Criteria

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

1. Has signed and dated an IRB/IEC-approved informed consent form before any protocol-specific screening procedures are performed.

2. Is a male or female aged 30 to 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.

3. Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the United Kingdom (UK) Brain Bank criteria, diagnosed after the age of 30 years.

4. Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.

5. Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.

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

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

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

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

8. Patients must have a ≥ 25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.
9. Patients must understand (with or without caregiver assistance) their daily medication regimen and must agree that they will not change their daily medication doses during the study.

10. Patients must have normal cognition as confirmed by a score of ≥ 25 on the Mini Mental State Examination (MMSE), performed in the ON state.

11. 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.

12. (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.)

8.2. Exclusion Criteria

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

1. Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures.

2. Pregnant or lactating females or females wishing to become pregnant.

3. Patients who have any known contraindication to the use of LD, including a history of malignant melanoma or a history of narrow-angle glaucoma.

4. Patients who have had previous surgery for PD (including but not limited to deep brain stimulation or cell transplantation) or plan to have stereotactic surgery during the study period.

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 14 for a list of contraindications).


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. Patients who have participated in any prior CVT-301 study, regardless of treatment group assignment.

15. 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 when he or she has completed all study visits through TV4 if the patient is continuing into the CVT-301-004E study or through the Follow-up Visit if that patient is not continuing into the CVT-301-004E study. A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. If a patient has a clinical necessity to alter their standard PD medications, the medical monitor should be consulted. 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 Early Termination Visit assessments as shown Appendix 9. 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. 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).

Patients who were withdrawn may not be re-entered into the study and may not enroll in the extension study.

9. **TREATMENTS**

9.1. **Details of Study Treatments**

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

**Table 1**: Details of Study Drugs

<table>
<thead>
<tr>
<th>Study Drugs To Be Administered</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVT-301 (Test Product)</td>
</tr>
<tr>
<td><strong>Name</strong></td>
<td>CVT-301 (levodopa inhalation powder)</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Civitas Therapeutics, Inc.</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>DL1: 2 CVT-301 capsules delivering a target nominal respirable dose of approximately 35 mg LD FPD</td>
</tr>
<tr>
<td></td>
<td>DL2: 2 CVT-301 capsules delivering a target nominal respirable dose of approximately 50 mg LD FPD</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Inhaled via the CVT-301 inhaler</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Capsules of levodopa inhalation powder</td>
</tr>
<tr>
<td><strong>Capsule Strength</strong></td>
<td><strong>DL1 capsule units</strong>: Capsule fill weight of LD: 30 mg (\text{Respirable LD dose/FPD per capsule: 17.5 mg (Emitted LD dose per capsule: 25 mg)})</td>
</tr>
<tr>
<td></td>
<td><strong>DL2 capsule units</strong>: Capsule fill weight of LD: 42 mg (\text{Respirable LD dose/FPD per capsule: 25.0 mg (Emitted LD per capsule: 35 mg)})</td>
</tr>
</tbody>
</table>

Abbreviations: DL1=Dose Level 1; DL2=Dose Level 2; FPD=fine particle dose; LD=levodopa; NF=National Formulary.
9.1.1. CVT-301 Capsule for Inhalation (Test Product)

CVT-301 is a white to off-white powder supplied by Civitas Therapeutics, Inc., in size 00 hypromellose (hydroxypropyl methylcellulose [HPMC]) capsules. See Table 1 for a description of the LD capsule fill weights, the emitted LD dose per capsule, and the target nominal respirable LD dose per capsule.

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

9.1.2. Placebo Capsule for Inhalation

The placebo inhalation powder is a white to off-white powder supplied by Civitas Therapeutics, Inc., in size 00 HPMC capsules, each at a nominal fill weight of 10 mg of inhalation-grade lactose, National Formulary (NF). Placebo capsules are packaged into blister strips composed of foil-foil blister strips.

9.1.3. Sham Capsule for Inhalation

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

9.1.4. Civitas CVT-301 Inhaler

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

9.1.5. Packaging of Blinded Inhaled Study Treatment

At TV1, TV2, and TV3, each randomized patient will be issued 4 study treatment kits (1 month supply) containing 20 blister strips of CVT-301 DL1, CVT-301 DL2, or placebo, 1 CVT-301 inhaler, and the IFU. Each kit is configured with an 8-day supply of study drug to provide an overage if necessary to accommodate maximal visit windows (e.g., a holiday weekend). 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 empty capsules, and all inhalers 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: [mailto:QualityClinicalComplaints@CivitasRx.com]. 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, eligibility criteria will be reviewed by delegated staff. Upon confirmation of eligibility from the external eligibility reviewer, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). Sites must leave a minimum of 5 days between randomization and Treatment Visit 1.

Patients will be randomized in a 1:1:1 ratio to receive either CVT-301 DL1, CVT-301 DL2, or placebo; randomization will be differentiated by the patient’s Hoehn and Yahr PD disease severity scale (<2.5 versus ≥ 2.5) to balance the severity of disease in each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥ 60% of predicted and FEV1/FVC ratio ≥ 70%). The IWRS will assign the appropriate study kits to each patient. The assigned kits will be sent to the site prior to the start of dosing of each patient.

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 CVT-301 and placebo groups.

The patient, investigator, and study site personnel, the Sponsor, 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 current study and the follow-on extension study (CVT-301-004E); 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, “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

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

Clinic staff will contact patients by telephone 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

Medications taken by or administered to the patient for 3 months prior to SV1 will be recorded in the eCRF. The patient’s oral LD-containing regimen must include at least 3 doses during the waking day, and this regimen must have been stable for at least 2 weeks prior SV1 when not including Rytary, and stable for at least 6 weeks prior to SV1 when including Rytary. The oral LD dose frequency, schedule, and dose level should remain stable for the duration of 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.

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.).

3. Patients meet all other eligibility criteria (including spirometry).

4. Patients must agree not to use medical marijuana (smoking, ingestion or any other potential route of administration) on clinic days, before coming into the clinic or while in the clinic, until all procedures have been completed and they are discharged.

Patients 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 add any new PD medications or take additional inhaled study medication during the study.

**Prohibited Medications**

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 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, in-clinic treatment visits, and the Follow-up Visit).

- Oral PRN PD medications. Patients are permitted to take oral PRN PD medications
during the screening period, but oral PRN PD medications are not permitted during
the treatment period.

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.
10. STUDY PROCEDURES

The overall schedule of assessments is provided in Appendix 1, and specific time and events schedules for screening, in-clinic treatment visits, and the Follow-up Visit are provided in Appendix 2 through Appendix 9. Unless otherwise specified, all assessments will be performed by the investigator or other assigned study 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 Appendix 2 through Appendix 9.

10.1.1. Screening Period

The screening period, which takes place within 35 days prior to randomization, will have 2 separate visits: Screening Visit (SV) 1 (SV1) and SV2 must be separated by at least 4 days. 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 that 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 (within 35 days prior to randomization)

Patients should be instructed to bring all of their medications with them to SV1. The patient will be evaluated for eligibility in ON and OFF states. 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 12.)
5. Use the modified Hoehn and Yahr scale to assess PD severity (in an ON state). (Refer to Appendix 13.)
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 semi-supine position for at least 5 minutes, and orthostatic vital signs should be taken after the patient has been standing for 2 minutes (see Section 11.1.2 for suggested detailed procedures).

13. Perform spirometry to measure FEV1, FVC, and FEV1/FVC ratio to assess lung function (this must be performed with the patient in the ON state).

14. Perform UPDRS Part 1, 2, 3 and 4 in an ON state.

15. Train patients (while in the ON state) 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 11 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 discrete 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.

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 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 requirements noted in Item 26 in the above list.

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

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

The following list is a suggested schedule for this visit:
1. Upon the patient’s arrival to the clinic, reconfirm eligibility, 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. Confirm the usual PD medication dose and regimen has not changed.

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 the ON state); full physical examination; 12-lead ECG; standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR); spirometry in ON and OFF states; UPDRS Part 3 (in ON and OFF states); UPDRS Part 1, 2 and 4, ON/OFF concordance testing (in ON and OFF states); and clinical laboratory tests, 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 and spirometry visit 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 (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. 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 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 3 days prior to TV1, this visit will be rescheduled once these symptoms have been resolved for at least 3 days.
10.1.2. Randomization to Study Drug and Scheduling Baseline DLco

Before patients return to the clinic for TV1, they will be randomized to treatment. Patients will not be randomized until the clinic staff has received confirmation of eligibility from the external eligibility reviewer (subjects requiring pulmonary adjudication may not be randomized until completion of pulmonologist review). Upon approval, an eligible patient will be randomized to receive CVT-301 DL1, CVT-301 DL2, or placebo in a 1:1:1 randomization scheme; randomization will be differentiated by the patient’s Hoehn and Yahr disease severity scale rating (<2.5 versus ≥ 2.5) to balance the severity of disease in each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥ 60% of predicted and FEV1/FVC ratio ≥ 70%).

Site staff must allow at least 5 days between date of randomization in the Interactive Web Response System (IWRS) and the date of TV1.

Refer to Section 9.2 for further randomization details.

10.1.3. Treatment Period

The study is designed to evaluate the effect of adjunctive therapy (CVT-301 plus usual prescribed standard PD medication regimen) compared with the usual standard of care (placebo 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 and should not alter this regimen during the study.

The treatment period includes 4 separate in-clinic visits over approximately 12 weeks. 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. For the duration of the study, a patient’s background PD medication regimen will not otherwise be changed. 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, CVT-301 DL2, or placebo) 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, CVT-301 DL2, or placebo); patients will be given study drug kits at TV1, TV2, and TV3.

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 to the original randomized dose level (i.e., 2 capsules). This return to
randomized dose must take place at the in-clinic visit only and may only be done once during the study. 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 not be eligible for any additional up-titration to the original dose.

Refer to Appendix 2 through Appendix 9 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 patients 4-6 days prior to TV1 for the following reasons: to confirm the DLco/spirometry assessments have been done or are scheduled to occur before TV1 (can be done any time after SV2); 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 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.

  - 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 within 4-6 days before TV2, TV3, and TV4 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 DLco and spirometry visit at the pulmonary function lab has taken place or is scheduled to occur (prior to TV3 and TV4 only); to confirm the next study visit; to remind patients to complete the PD Diaries for the 3 consecutive days prior to TV2, TV3, and TV4; 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; and to remind them to note the time when they take these morning medications.
10.1.3.2. Treatment Visit 1 (Baseline; 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 for baseline assessments (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 pulmonary lab visit (DLco, slow vital capacity and spirometry assessments) has been performed. If these assessments at the pulmonary lab have 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.
- Confirm that the usual PD medication dose/regimen has not changed.
- Record all concomitant medications.
- Patient will complete the PDQ-39 and PHQ-9 in an ON state.
- Perform a brief physical examination.
- 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).
- 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 pregnancy test, if applicable. Document fasting status.
- Perform the baseline assessments using 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 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, and TV4).

- 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 12-week treatment period.

- Distribute study drug kits to patients. Each patient will receive 4 study drug kits (with an 8-day supply per kit). 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 that were provided (i.e., 2 capsule inhalations of either CVT-301 DL1, CVT-301 DL2, or placebo). Patients will be permitted sips of water between capsule inhalations, as needed. The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.

Note: Instructions for how to properly use the CVT-301 system are outlined in the Instructions for Use document that is included with every CVT-301 study kit. Refer to Appendix 16 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 15 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 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 4 to 6 days before each visit for TV2, TV3, and 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 taken place or is scheduled to take place (prior to TV3 and TV4 only), to confirm the next study 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. At-Home Dosing

At TV1, TV2, and TV3, patients will receive study drug kits and the IFU to take home with them. Patients will be instructed to take their standard oral PD medications as prescribed on their usual schedule of administration, which will not be modified during the 12 weeks of study drug treatment.

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.

In the event that an OFF state is not sufficiently resolved within 45 minutes of completing the last capsule inhalation, patients should 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. Also, they may not add any new PD medications during the study nor alter their usual PD medication dose or dose regimen during the study.

Patients will complete the PD Diary for the 3 consecutive days prior to TV2, TV3, and TV4. Patients will complete the Inhaled Dosing Log every day during the 12-week treatment period. As described previously, patients will be contacted by the clinic staff 1 to 3 days after TV1 and 4 to 6 days prior to each visit for TV2, TV3, and TV4. They 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 visits.

10.1.3.4. Treatment Visit 2 (Week 4, 28±5 days after TV1)

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.
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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Record the time that patients took their usual PD medications prior to the visit.
- Confirm that there were no changes in the usual PD medication dose/regimen.
- Collect used empty capsules and inhalers and unused supplies.
- 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 BP, HR, and RR and orthostatic BP and HR.
- 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. Each patient will receive 4 study drug kits (with an 8-day supply per kit).
- Review inhaler training with the patient (if needed).
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
• Observe the patient for the appearance of dyskinesia and note in the 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 during the 60-minute post-dose period.

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

• Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.

• Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.

• 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).

Clinic staff will arrange to speak with patients by telephone 4 to 6 days before TV3 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done, to confirm the next study visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule the DLco and spirometry visit at the pulmonary function lab for 14±3 days after TV2. 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.

10.1.3.5. Treatment Visit 3 (Week 8, 56±5 days after TV1)

Patients will complete the PD Diary for 3 consecutive days prior to TV3, and patients will complete the Inhaled Dosing Log daily throughout the treatment period. They will bring 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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

The following procedures will be done:

• Confirm that the DLco and spirometry visit at the pulmonary function lab was completed prior to the visit. If these assessments were not completed prior to the visit, the study visit must be re-scheduled.
- Collect, review, sign, and date the PD Diary and Inhaled Dosing Log.
- Record the time that patients took their usual PD medications prior to the visit.
- Confirm that there were no changes in the usual PD medication dose/regimen.
- Collect used empty capsules and inhalers and unused supplies.
- 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 a brief physical examination.
- Record standard BP, HR, and RR and orthostatic BP and HR.
- 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. Each patient will receive 4 study drug kits (with an 8-day supply per kit).
- Review inhaler training with the patient (if needed).
- The patient will remain in the clinic until they go into the OFF state. After confirmation of an OFF state (between 2 and 5 hours after the patient has taken his/her oral PD medication), record the time of the OFF state and then perform a pre-dose UPDRS Part 3 assessment. Under clinic staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia, and note in the 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 during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Distribute the PD Diary and Inhaled Dosing Log and review instructions for completion.
• Instruct patients to collect used empty capsules, the PD Diary, Inhaled Dosing Log, and other study supplies and to bring these items to the next visit.

• 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).

Clinic staff will arrange to speak with patients by telephone 4 to 6 days before TV4 to address any concerns or challenges with the inhaler systems, PD Diary, or Inhaled Dosing Log, to monitor for any AEs, to confirm the DLco assessment has been done/scheduled, to confirm the next study visit, and to remind patients of the study procedures required before the next visit (including completion of the PD Diary and Inhaled Dosing Log). Clinic staff will also schedule the DLco and spirometry visit at the pulmonary function lab for 7±3 days before 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.

10.1.3.6. Treatment Visit 4 (Week 12; 84±5 days after TV1)

Patients will return to the clinic for TV4 approximately 12 weeks (84±5 days) after TV1, and this visit will constitute the end-of-treatment visit.

Patients will record their use of inhaled study medication each day up to TV4 in the Inhaled Dosing Log and complete the PD Diary during the 3 consecutive days prior to TV4. They will bring the PD Diary, Inhaled Dosing Log, used empty capsules and inhalers, and 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 for baseline assessments (i.e., they should arrive to the clinic as shortly as feasible after taking their standard oral PD medications at home). Patients will bring to the clinic all usual PD medications.

Upon arrival, the following will be performed:

• Confirm that the DLco and spirometry visit at the pulmonary function lab was completed prior to the visit. If these assessments were not completed prior to the visit, the study visit must be rescheduled.

• Collect, review, sign, and date of the PD Diary and Inhaled Dosing Log.

• Confirm that there were no changes in the usual PD medication dose/regimen and record the time of the patient’s prior usual PD medication and dose.

• Collect the empty capsules, inhalers, and any unused supplies.

• Record concomitant medications.
- Patient will complete the PDQ-39, PHQ-9 and PGI-C scale (in the ON state).
- Complete the UPDRS Part 2 and S&E ADL (preferably in the ON state).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform brief physical examination.
- Perform the C-SSRS, Epworth Sleepiness Scale, and QUIP (preferably in the ON state).
- Patient will complete the Impact of Parkinson’s OFF Episodes Patient Survey (preferably in an ON state)
- Record standard vital signs (BP, HR, and RR) and orthostatic vital signs (BP and HR).
- Perform a 12-lead ECG.
- Provide a new inhaler for study drug administration. Patients will use blinded study drug from the supplies brought to the visit.
- The patient will remain in the clinic until they go into the OFF state. In the OFF state (confirmed by the investigator and between 2 and 5 hours after their prior oral PD medication), immediately pre-dose, patients will undergo UPDRS Part 3 assessments. Under staff supervision, patients will prepare and self-administer their entire dose of inhaled study drug (CVT-301 DL1, CVT-301 DL2, or placebo). The dosing time is defined to be when the patient’s OFF state is recognized by both the patient and investigator to be at a level similar to the investigator-confirmed severity experienced at SV1 and preferably between 2 and 5 hours after their prior oral PD medication.
- Perform serial UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post-dose.
- Observe the patient for the appearance of dyskinesia, and note in the 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 during the 60-minute post-dose period.
- Observe the patient for the occurrence of an ON state during the 60-minute post-dose period and note whether this occurs. If the patient converts to the ON state, note whether or not the patient is still in the ON state at 60 minutes post-dose.
- Patients will undergo clinical laboratory tests (with documentation of fasting status) including a serum pregnancy test, if applicable.
- Monitor for AEs throughout the visit.
- Provide patients with a full explanation of the purpose and nature of the extension study (CVT-301-004E). Patients who plan to enroll may sign consent for the extension study. Patients who do not enter the CVT-301-004E study should be scheduled to return for the Follow-up Visit (see Section 10.1.4).
If the patient is in an OFF state 60 minutes after inhalation, patients will resume their standard oral dose of PD medication and be discharged from the clinic after adequate motor function resumes and all scheduled study procedures have been completed.

As described previously, patients who successfully complete the study through TV4 will be offered the opportunity to consent to a long-term (12-month) treatment extension study (CVT-301-004E) and study visits will be scheduled in accordance with that protocol. Eligibility for CVT-301-004E will be based, in part, on successful completion of study procedures, including completion of the final DLco and spirometry visit, which for continuing subjects takes place before TV4.

Patients who are not entering the CVT-301-004E study will return for the Follow-up Visit, described in Section 10.1.4.

### 10.1.4. Follow-up Visit (7-14 days after TV4 for patients not continuing in the extension study [CVT-301-004E])

Patients who are not entering the long-term extension study, CVT-301-004E, will return for the Follow-up Visit 7-14 days after TV4. The following assessments will be performed:

- Confirm that the patient has continued to be on a stable regimen of PD medications.
- Record AEs and concomitant medications.
- 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.
- Clinical laboratory tests (with documentation of fasting status).
- Complete the UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).
- Perform the C-SSRS, Epworth Sleepiness Scale, and the QUIP (preferably in an ON state)

### 10.1.5. Early Termination Visit

If a patient withdraws early from the study, the assessments for the Follow-up Visit (see Section 10.1.4) will be performed. If the termination occurs prior to TV4, then the following are also required in addition to the assessments for the Follow-up Visit (Section 10.1.4): collect, review, sign, and date the PD Diary and Inhaled Dosing Log; collect empty capsules, inhalers, and unused supplies; PDQ-39, PHQ-9 and PG1-C (preferably in ON state); UPDRS Part 2; UPDRS Part 4 (Questions 32-35 and 36-39); S&E ADL; C-SSRS, Epworth Sleepiness Scale; QUIP, and Impact of Parkinson’s OFF Episodes Patient Survey (preferably in the ON state). If the early termination is after the start of treatment and more than 14 days following any post-treatment DLco and spirometry visit, these assessments will be performed as close to the time of study withdrawal as possible.
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:

- If concordance is not reached during SV1, the same training and testing may be repeated at an unscheduled visit between SV1 and SV2 or at SV2. If patients return for an unscheduled visit between SV1 and SV2 for concordance training and testing, the visit must occur more than 3 days prior to SV2.

- If a patient is unable to complete a screening assessment at SV2 (repeat SV2), an additional visit may be scheduled prior to eligibility determination and randomization. Any repeat assessments should be performed in the respective motor state as described for SV1.

- If a patient develops significant tolerability concerns that in the opinion of the investigator are of a severity that should necessitate a reduction in dose, including, but not limited to, exacerbation or worsening of troublesome dyskinesia, other problematic dopaminergic symptoms, or other tolerability concerns, a dose reduction (from 2- to 1-capsule inhalation per dose) will be permitted. The medical monitor should be contacted, and the investigator should use his/her clinical judgment to determine if an additional unscheduled visit is required and what assessments should be performed (e.g., physical examination, spirometry, etc.).

11. DESCRIPTION OF ASSESSMENTS

11.1. Safety Assessments

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

11.1.1. Physical Examination

A complete physical examination (head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening. 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 each treatment period visit (prior to dosing) and at the Follow-up Visit. 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 AE.
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 SV1 (or SV2) and each of the subsequent study visits, 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/tablesise 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 9 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 11. 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 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), TV1, and TV4 or the Early Termination Visit, 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 be reviewed by a central spirometry laboratory which will provide a quality over-read of all evaluations based on acceptability and repeatability metrics in accordance with ATS criteria (Miller et al., 2005). FEV1, FVC and FEV1/FVC ratio will be recorded from the single “best test” (based on effort with highest summed FEV1 and FVC). Variables and comparisons will include the actual and expected forced FEV1, FVC, and FEV1/FVC ratio. Patients with FEV1 <50% of predicted for race, age, sex, and height, or FEV1/FVC ratio ≤ 60% in the ON state at screening will be excluded from the study. A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥ 50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% at screening in order to determine eligibility. Patients with an FEV1/FVC ratio that is >60% to <70% at screening will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/ERS criteria. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization. Any subject requiring pulmonary adjudication at screening will not be randomized until after full pulmonologist review.

Spirometry assessments will be done at the study visits and time points indicated in Appendix 2 through Appendix 9. 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 at SV1, SV2 (if necessary) and TV1. 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.

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), before TV3, and before TV4, as described in Appendix 2 through Appendix 9. 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.

All DLco data collected at pulmonary function labs will be sent to and reviewed by a central Pulmonary Function Testing reviewer.

### 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 SV1, worsens during the study, regardless of the suspected cause of the event. Changes in conditions present at SV1 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, AEs reported during the period from informed consent 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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.</td>
</tr>
<tr>
<td>MODERATE</td>
<td>An event that is sufficiently discomforting to interfere with normal everyday activities.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>An event that prevents normal everyday activities.</td>
</tr>
</tbody>
</table>
Table 3  Classification of Adverse Events by Relationship to Study Medication

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely not related</td>
<td>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).</td>
</tr>
<tr>
<td>Unlikely related</td>
<td>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.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>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.</td>
</tr>
<tr>
<td>Probably related</td>
<td>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.</td>
</tr>
<tr>
<td>Definitely related</td>
<td>This designation should be reserved for those events which have no uncertainty in their relationship to treatment administration.</td>
</tr>
</tbody>
</table>

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 INC Pharmacovigilance Group and will be communicated to the Sponsor. **Any such SAE due to any cause, whether or not related to the study medication, must be reported within**
24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using the dedicated fax line for the

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 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) will only be assessed at screening, and all treatment visits, follow-up visit, or the Early Termination Visit, if applicable.

Additionally, during the post-dosing follow up period at TV2, TV3, and TV4, 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 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-Suicidality Severity Rating Scale

The C-SSRS is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. An initial baseline version will be given at SV2 and TV1 (baseline), and a “since last visit” version will be given at all subsequent study visits to detect any emergence of suicidal ideation or behavior. The clinic staff should address any emerging neuropsychiatric needs in the event that the C-SSRS indicates active suicidal ideation.

11.1.12.3. Epworth Sleepiness Scale

The Epworth Sleepiness Scale is used to determine the level of daytime sleepiness. There are 8 situations listed (e.g., sitting and reading, watching television) for which patients rate their likelihood of dozing or sleeping (0 = would never doze or sleep, 1 = slight chance of dozing or sleeping, 2 = moderate chance of dozing or sleeping, and 3 = high chance of dozing or sleeping). A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy. Patients will be assessed at SV2 and all treatment visits, the follow-up visit, and at the Early Termination Visit, if applicable.

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. Patients will be assessed at SV2 and at all treatment visits, the follow-up visit, and at the Early Termination Visit, if applicable.

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:

- UPDRS Part 3 motor score
- Occurrence of an ON state during the 60-minute post-dose period and if an ON state occurs during the 60-minute post-dose, whether or not the patient is still in the ON state at 60 minutes post-dose
- 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, TV1, TV2, TV3, and TV4, 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 SV1, SV2, TV1, TV2, and TV3 and patients will bring the completed diaries to the clinic at SV2, TV1, TV2, TV3, and TV4. Information in the diaries will be reviewed and recorded by clinic staff.

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

For the 3 consecutive days prior to SV2 and TV1, patients will record the discrete number of OFF episodes experienced by the patient during their waking day in the Screening ON/OFF Episodes Log.

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, signed, and dated 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, and TV3, and patients will bring the completed logs to the clinic at TV2, TV3, and TV4. 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 familiarize the patient with the study evaluations as well as to document each patient’s response to his/her own PD medications; to enter the study, the difference between UPDRS Part 3 scores in the ON and OFF states must be ≥ 25%.

The percent difference is calculated as follows:

\[
\text{Percent Difference} = \frac{\text{UPDRS III value in OFF state} - \text{UPDRS III value in ON state}}{\text{UPDRS III value in OFF state}}
\]

UPDRS Part 3 assessments will be done at TV2, TV3, and TV4, immediately before and at various time points after study medication dosing, as indicated in the time and events tables in Appendix 2 through Appendix 9.
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 at all treatment visits or the Early Termination Visit, if applicable.

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. Patients will be assessed in the ON state at all treatment visits or the Early Termination Visit, if applicable.

11.2.5. 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.

11.2.6. 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 scale will be completed in the ON state at TV2, TV3, and at TV4 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 at all treatment visits or the Early Termination Visit (if applicable), preferably while the patient is in the ON state.

11.2.8. UPDRS Part 2

The UPDRS Part 2 is an evaluation of the ADL; this will be assessed by a qualified rater at screening and all treatment visits, or the Early Termination Visit (if applicable), preferably while the patient in the ON state.
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 12 and discussed in Hughes (1992).

11.3.2. **Modified Hoehn and Yahr PD Disease Severity Assessment**

PD severity will be staged using the modified Hoehn and Yahr disease severity scale (refer to Appendix 13).

11.3.3. **UPDRS Part 1**

The UPDRS Part 1 assesses the non-motor impact of Parkinson's disease (PD) on patients’ experiences of daily living, and will be part of the baseline characterization of the patient (not used to determine eligibility).

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. 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 (e.g., UPDRS Part 3 motor score assessments). 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 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 prior to the unblinding of the randomization codes. The SAP will serve as a compliment to the protocol and supersedes it in case of differences. Because of the unpredictability of some problems, it may be necessary to decide the manner with which irregularities will be dealt in a blind data review meeting before breaking the blind.

12.1. Determination of Sample Size

The sample size of the study is based on the primary variable of the study: the change in the UPDRS Part 3 score at 30 minutes post-dose. The study has been powered to detect a difference of 5 points in the mean change in the average UPDRS Part 3 score, assuming a standard deviation of 10.0 points. To achieve a power of 90%, a total of 86 patients per group are required using a two-sided significance level of 0.05. To account for a drop-out rate of approximately 25%, 115 patients per group will be randomized. In the event that the withdrawal rate exceeds 25%, additional patients may be enrolled to ensure that at least 258 patients complete the study.

12.2. Study Populations

The safety and intent-to-treat (ITT) populations will include all patients who receive at least 1 dose of inhaled CVT-301 or placebo. The safety population will be grouped by the actual dose level that the patient received while the ITT population will be grouped by the randomized dose level. The All available population (AAP) will include all patients who have consented for the study, including screening failures.

12.3. 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.

12.4. 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 the study treatment will be summarized by tabulating the number of patients being exposed to each dose level.

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 both by treatment group (CVT-301 or placebo) and by dose level (CVT-301 DL1, CVT-301 DL2, or placebo).

For vital signs, ECG parameters, spirometry, and DLco, 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, DLco, and safety laboratory variables, the differences in pre-dose values between study days will be compared using descriptive statistics and by tabulating the proportion of normal and abnormal values and/or potentially clinically significant values or changes in parameters. 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<sup>1/2</sup>) and QTcF (Fridericia's correction formula calculated as QT/RR<sup>1/3</sup>). 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.

For suicidality, somnolence, and impulse-control disorders, the change from baseline (TV1 pre-dose) to TV4 or Early Termination Visit will be presented using descriptive statistics.
12.4.1. Interim Safety Data Review

Safety data will be reviewed by a DSMC that will include relevant medical experts (including a neurologist and pulmonologist), an independent statistician, and additional representatives (as will be defined in the DSMC Charter). Safety data, including but not limited to AEs, spirometry, vital signs, and ECG data will be reviewed. The safety review will be documented in a DSMC Charter prior to the start of the study. In the event that potential safety issues are identified, the committee may recommend modification of the study design or study termination, which will be communicated promptly with investigators, IRBs, IECs, and regulatory agencies, in accordance with legal and regulatory requirements. There will be no prospective interim evaluation of efficacy endpoint data.

12.5. Efficacy Analysis

12.5.1. Primary Efficacy Endpoints

The primary endpoint of the study is the change from pre-dose in the UPDRS Part 3 score at 30 minutes post-dose. The primary endpoint of the study will be based on the evaluation of this assessment at TV4.

The UPDRS Part 3 total score will be calculated as the sum of the individual items of the UPDRS Part 3 questionnaire (UPDRS items 18-31) separately at each time point. Missing individual items will be imputed using the 2 non-missing values at time points adjacent to the missing item on the same date. The maximum of the 2 adjacent values will be assigned as the score for the missing item. However, pre-dose values will not be assigned as post-dose values and if one of the adjacent values for a post-dose value is a pre-dose value, only 1 adjacent value will be used. The total score for UPDRS Part 3 assessments will be calculated after imputation of the missing item(s). If a pre-dose value is missing, the pre-dose value at the prior visit will be used. A missing TV2 pre-dose value will be imputed using the last screening value in OFF state.

The differences between CVT-301 DL1, CVT-301 DL2, and placebo at TV4 in the primary variable will be estimated using a Mixed Model for Repeated Measurements (MMRM) with contrasts. The model will include the treatment group (CVT-301 DL1, CVT-301 DL2, or placebo), visit (TV2, TV3, or TV4), the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) and the interaction between the treatment group and visit as fixed factors. The OFF-state baseline UPDRS part 3 score will be included as a covariate. An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) or the heterogeneous Toeplitz structure (TOEPH) will be used instead. If the unstructured covariance structure will be used, the denominator degrees of freedom will be computed using the Kenward-Roger method. In case of other covariance structures, the BETWITHIN option will be used for the denominator degrees of freedom.

The primary and secondary objectives will be tested using a hierarchical approach. The order of the testing is outlined below. See Section 6 for the definition of the primary and secondary objectives.

1. Primary objective: DL2 versus placebo
2. Secondary objective #1: DL2 versus placebo
3. Secondary objective #2: DL2 versus placebo
4. Secondary objective #3: DL2 versus placebo
5. Secondary objective #4: DL2 versus placebo
6. Secondary objective #5: DL2 versus placebo
7. Primary objective: DL1 versus placebo
8. Secondary objective #1: DL1 versus placebo
9. Secondary objective #2: DL1 versus placebo
10. Secondary objective #3: DL1 versus placebo
11. Secondary objective #4: DL1 versus placebo
12. Secondary objective #5: DL1 versus placebo

First, the objective ranked as first will be tested and the difference will be declared statistically significant if the nominal p value is less than 0.05. Second, in case that the difference for the first objective is statistically significant, the objective ranked as second will be tested, and the difference will be declared statistically significant if the nominal p-value is less than 0.05. The testing will continue as long as the previously ranked objective was statistically significant.

An additional secondary objective (objective related to the time-course of the change from pre-dose in the UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes post-dose at TV4) will be evaluated regardless of the hierarchical testing procedure. In case all objectives are not evaluated as a part of the hierarchical testing procedure, the statistical tests will be reported in any case and interpreted in a descriptive manner.

The sensitivity analyses will be specified in the SAP. Sensitivity analysis will be performed at least for the method to handle missing data (e.g., last observation carried forward, pattern mixture model using multiple imputation), definition of analysis population (e.g., patients completing TV3 and TV4) and statistical method (e.g., ANCOVA models separately for each visit).

12.5.2. Secondary Efficacy Endpoints

The secondary objectives, as described and ranked in Section 6, will be tested using a hierarchical approach, see Section 12.5.1. The derivation of the endpoints related to the secondary objectives and additional secondary objectives will be defined in detail in the SAP.

The continuous secondary endpoints will be analyzed using MMRM model similar to the one used for the primary endpoint. For continuous variables which include pre-treatment baseline assessments, the baseline assessment will be included as a covariate in the model instead of the OFF-state baseline UPDRS part 3 score.

The categorical endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC). Each visit will be tested separately. In case of missing data, the last value will be carried forward for the categorical endpoints.
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 will supply the Sponsor with the following documents:

- Original, signed 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.
14. REFERENCES


Oleson L, Turncliff RZ, Silberman B, Fogarty C, Ehrich E. ALKS 27 (Trospium Inhalation Powder) improves lung function following single administration in subjects with COPD. Am J Respir Crit Care Med 2010; 181:A4457.


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Appendix 1: Overall Visit Schedule Schematic

Abbreviations: DL1 = dose level 1; DL2 = dose level 2; DLco = carbon monoxide diffusing capacity; SV = screening visit; TV = treatment visit; W = week.
### Appendix 2: Time and Events Table—Screening Visit 1 (SV1; within 35 days prior to randomization)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>At arrival (assess in ON or OFF state)</th>
<th>Assess in ON state</th>
<th>Assess in OFF state</th>
<th>End of SV1</th>
<th>Post-SV1 Telephone Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility according to inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history including PD history and smoking history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm PD diagnosis and severity (UK Brain Bank/Modified Hoehn and Yahr scale)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record average number of hours OFF during waking</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD medications (confirm as stable)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full physical examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Function Baseline Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 3</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 1, 2, and 4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient training on self-report of ON/OFF states</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ON/OFF Concordance testing³</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory tests (including serum pregnancy test, if applicable)⁴</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaler training using sham capsules</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. ON or OFF state, 2. Assess in ON state, 3. X, 4. Y
### Procedures

<table>
<thead>
<tr>
<th>Procedures</th>
<th>At arrival (assess in ON or OFF state)</th>
<th>Assess in ON state</th>
<th>Assess in OFF state</th>
<th>End of SV1</th>
<th>Post-SV1 Telephone Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribute PD Diary and Screening ON/OFF Episodes Log and review instructions for completion</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Monitor for AEs</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Post-SV1 telephone contact: call patient ~4 days prior to SV2</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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; at least 4 days after SV1)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>At arrival (assess in ON or OFF state)</th>
<th>Assess in ON state</th>
<th>Assess in OFF state</th>
<th>End of SV2</th>
<th>Post-SV2 DLco Test</th>
<th>Post-SV2 Telephone Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm eligibility: Review completed PD Diary and Screening ON/OFF Episodes Log²</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD medications (confirm stable) and other concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaler training using sham capsules and IFU³</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient training on assessment of ON/OFF state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-CSSR</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUIP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribute PD Diary and Screening ON/OFF Episodes Log and review instructions for completion³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Monitor for AEs</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-SV2 DLco and spirometry visit¹ (after SV2 and before TV1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Post-SV2 telephone contact: call patient 4-6 days prior to TV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

#### Screening procedures from SV1 that can be completed/repeated at SV2, if necessary:

<table>
<thead>
<tr>
<th>Procedures</th>
<th>At arrival (assess in ON or OFF state)</th>
<th>Assess in ON state</th>
<th>Assess in OFF state</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full physical examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 3</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 1, 2, and 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ON/OFF Concordance testing</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory tests (including serum pregnancy test, if applicable)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Procedures appear in the table in the preferred order of completion.
2Refer to Section 10.1.1.2 of protocol for management of incorrect or incomplete patient diaries.
3If 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.
4The PD Diary and Screening ON/OFF Episodes Log are to be completed for the 3 consecutive days prior to TV1.
5Assessment to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
6Document whether patient is fasting (≥ 4 hours after last snack or meal).
### Appendix 4: Time and Events Table—Treatment Visit 1 (TV1; Day 1 of study drug; at least 7 days after SV2)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Arrival</th>
<th>Pre-dose</th>
<th>Time 0 (Dosing)</th>
<th>10 min Post-dose</th>
<th>15 min Post-dose</th>
<th>20 min Post-dose</th>
<th>30 min Post-dose</th>
<th>60 min Post-dose</th>
<th>End of TV1</th>
<th>Post-TV1 Telephone Contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect, review, sign, and date Screening ON/OFF Episodes Log and PD Diary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Confirm that DLco and spirometry assessments are completed prior to visit; if not done, the study visit must be re-scheduled</td>
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## Procedures

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<th>15 min Post-dose</th>
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<th>30 min Post-dose</th>
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<td>Post-TV1 telephone contact: call patient 4-6 days before TV2</td>
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</table>

1 Perform procedures in the order shown in the table if they occur at the same post-dose time point.
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.
Procedures can be done at any point after arrival and before dosing.

Preferably in the ON state.

Document whether patient is fasting (≥ 4 hours after last snack or meal).

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 TV4.
### Appendix 5: Time and Events Table—Treatment Visit 2 (TV2; Week 4, 28±5 days after TV1)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Arrival</th>
<th>Pre-dose</th>
<th>Time 0 (Dosing)</th>
<th>10 min Post-dose</th>
<th>20 min Post-dose</th>
<th>30 min Post-dose</th>
<th>60 min Post-dose</th>
<th>End of TV2</th>
<th>Post-TV2 Telephone Contact</th>
<th>Post-TV2 DLco/spirometry</th>
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<td>Record time of patient’s prior usual PD medication dose</td>
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<tr>
<td>Confirm no changes in usual PD medication dose/regimen</td>
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<td>X</td>
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<td>Collect empty capsules, inhalers, unused supplies</td>
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<td>Record any changes in concomitant medications</td>
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<td>PGI-C (in ON state)</td>
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<td>Physical examination, brief</td>
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<td>Time 0 (Dosing)</td>
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<td>20 min Post-dose</td>
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<td>60 min Post-dose</td>
<td>End of TV2</td>
<td>Post-TV2 Telephone Contact</td>
<td>Post-TV2 DLco/spirometry</td>
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<td>Distribute PD Diary and Inhaled Dosing Log; review instructions for completion</td>
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 superscript: ¹ = 10 min post dose ² = Vital signs ³ = 20 min post dose ⁴ = 30 min post dose ⁵ = 60 min post dose
Procedures | Arrival | Pre-dose | Time 0 (Dosing) | 10 min Post-dose | 20 min Post-dose | 30 min Post-dose | 60 min Post-dose | End of TV2 | Post-TV2 Telephone Contact | Post-TV2 DLco/spirometry |
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
Post-TV2 telephone contact: call patient 4-6 days before TV3 | | | | | | | | | | | X |
Post-TV2 DLco and spirometry visit (14±3 days after TV2) | | | | | | | | | | | X |

1Dosing 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.

2Assessment can be done at any point after arrival and before dosing.

3Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

4The PD Diary is to be completed for the 3 consecutive days prior to TV3; the Inhaled Dosing Log is to be completed daily through TV4.

5Assessment to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
Appendix 6: Time and Events Table—Treatment Visit 3 (TV3; Week 8, 56±5 days after TV1)

<table>
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<th>30 min Post-dose</th>
<th>60 min Post-dose</th>
<th>End of TV3</th>
<th>Post-TV3 Telephone Contact</th>
<th>Post-TV3 DLco/spirometry Assessment</th>
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<td>Collect empty capsules, inhalers, unused supplies</td>
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<td>Record any changes in concomitant medications</td>
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<tr>
<td>UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)</td>
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<tr>
<td>Physical examination, brief</td>
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<td>Time 0 (Dosing)</td>
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<td>30 min Post-dose</td>
<td>60 min Post-dose</td>
<td>End of TV3</td>
<td>Post-TV3 Telephone Contact</td>
<td>Post-TV3 DLco/spirometry Assessment</td>
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<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td>X²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth sleepiness scale (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUIP (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of Parkinson’s OFF Episodes Patient Survey (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribute study drug kits</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Review inhaler training (if needed)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 3</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-administration of study drug (in OFF state)</td>
<td>X¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor for dyskinesia and ON/OFF states</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribute PD Diary and Inhaled Dosing Log and review instructions for completion²</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Monitor for AEs</td>
<td>X</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-TV3 telephone contact: call patient 4-6 days before TV4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>DLco and spirometry visit (7±3 days before TV4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Version 5.0
1Dosing 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.

2Assessment can be done at any point after arrival and before dosing.

3Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.

4The PD Diary is to be completed for the 3 consecutive days prior to TV4; the Inhaled Dosing Log is to be completed daily through TV4.

5Assessment to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
## Appendix 7: Time and Events Table—Treatment Visit 4 (TV4; Week 12, 84±5 days after TV1)

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Arrival</th>
<th>Pre-dose</th>
<th>Time 0 (Dosing)¹</th>
<th>10 min Post-dose</th>
<th>20 min Post-dose</th>
<th>30 min Post-dose</th>
<th>60 min Post-dose</th>
<th>End of TV4 Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm that the Post-TV3 DLco and spirometry assessment have been completed prior to visit; if not done, the study visit must be re-scheduled</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect, review, sign, and date PD Diary and Inhaled Dosing Log</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record time of patient’s prior usual PD medication dose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm no changes in usual PD medication dose/regimen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect empty capsules, inhalers, unused supplies</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record any changes in concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQ-39 (in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9 (in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGI-C (in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 2 (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S&amp;E ADL (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination, brief</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUIP (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of Parkinson’s OFF Episodes Patient Survey (preferably in ON state)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹: Time 0 (Dosing) refers to the time of dosing following the pre-dose procedures.
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Arrival</th>
<th>Pre-dose</th>
<th>Time 0 (Dosing)¹</th>
<th>10 min Post-dose</th>
<th>20 min Post-dose</th>
<th>30 min Post-dose</th>
<th>60 min Post-dose</th>
<th>End of TV4 Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td></td>
<td>X²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td>X²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide new inhaler for study drug administration</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Part 3</td>
<td></td>
<td>X¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Self-administration of study drug (in OFF state)</td>
<td></td>
<td>X¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Monitor for dyskinesia and ON/OFF states</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory tests (including serum pregnancy test, if applicable)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Monitor for AEs</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide explanation for extension study CVT-301-004E/sign consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Schedule Follow-up Visit for patients not enrolling in extension study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹Dosing 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.
²Assessment can be done at any point after arrival and before dosing.
³Confirm patient is in the OFF state prior to pre-dose UPDRS Part 3 assessment.
⁴Document whether patient is fasting (≥ 4 hours after last snack or meal)

**Version 5.0**
### Appendix 8: Time and Events Table—Followup Visit (7-14 days after TV4, for patients who do not continue on to extension study \textbf{[CVT-301-004E]})

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm that patient has continued to be on a stable regimen of PD medications</td>
<td>X</td>
</tr>
<tr>
<td>Record any changes in concomitant medications</td>
<td>X</td>
</tr>
<tr>
<td>Record any AEs</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination, brief</td>
<td>X</td>
</tr>
<tr>
<td>UPDRS Part 4 (Questions 32-35 and 36-39)</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
</tr>
<tr>
<td>Clinical laboratory tests\textsuperscript{1}</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS (preferably in ON state)</td>
<td>X</td>
</tr>
<tr>
<td>Epworth sleepiness scale (preferably in ON state)</td>
<td>X</td>
</tr>
<tr>
<td>QUIP (preferably in ON state)</td>
<td>X</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Document whether patient is fasting ($\geq 4$ hours after last snack or meal).
### Appendix 9: Time and Events Table—Early Termination Assessments

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect, review, sign, and date PD Diary, and Inhaled Dosing Log</td>
<td>X</td>
</tr>
<tr>
<td>Confirm that patient has continued to be on a stable regimen of PD medications</td>
<td>X</td>
</tr>
<tr>
<td>Collect empty capsules, inhalers, unused supplies</td>
<td>X</td>
</tr>
<tr>
<td>Record any changes in concomitant medications</td>
<td>X</td>
</tr>
<tr>
<td>PDQ-39 (preferably in ON state)²</td>
<td>X</td>
</tr>
<tr>
<td>PHQ-9 (preferably in ON state)³</td>
<td>X</td>
</tr>
<tr>
<td>PGI-C (preferably in ON state)³</td>
<td>X</td>
</tr>
<tr>
<td>UPDRS Part 2 (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>UPDRS Part 4 (Questions 32-35 and 36-39) (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>S&amp;E ADL (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>C-SSRS (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>QUIP (preferably in the ON state).</td>
<td>X</td>
</tr>
<tr>
<td>Impact of Parkinson’s OFF Episodes Patient Survey (preferably in the ON state)</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination, brief</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs (standard BP, HR, and RR and orthostatic BP and HR)</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
</tr>
<tr>
<td>Clinical laboratory tests (including serum pregnancy test, if applicable)²</td>
<td>X</td>
</tr>
<tr>
<td>Record any AEs</td>
<td>X</td>
</tr>
<tr>
<td>Schedule DLco and spirometry visit, if required³</td>
<td>X</td>
</tr>
</tbody>
</table>

1If the patient terminates prior to TV4.

2Document whether patient is fasting (≥ 4 hours after last snack or meal).

3Only required if the early termination is after the start of treatment and more than 14 days from any post-treatment DLco. This is to be performed in an ON state as close to the time as withdrawal as possible. This is to be performed in a dedicated pulmonary facility and includes slow vital capacity maneuver, DLco, and spirometry.
Appendix 10: 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 11: Laboratory Parameters

## Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RBC Indices:</th>
<th>Automated WBC Differential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>RBC Count</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>RBC Count</td>
<td>MCV</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>WBC Count (absolute)</td>
<td>MCH</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
<td>MCHC</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>Basophils</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Clinical Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>Potassium</td>
<td>AST (SGOT)</td>
<td>Total and direct bilirubin</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Chloride</td>
<td>ALT (SGPT)</td>
<td>Uric Acid</td>
</tr>
<tr>
<td>Glucose</td>
<td>Total CO₂</td>
<td>GGT</td>
<td>Albumin</td>
</tr>
<tr>
<td>Sodium</td>
<td>Calcium</td>
<td>Alkaline phosphatase</td>
<td>Total Protein</td>
</tr>
</tbody>
</table>

## Other screening tests

- Pregnancy test (serum) at SV1 or SV2 (if not obtained at SV1), and TV1 and TV4 or the Early Termination Visit
Appendix 12: 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

Appendix 13: Modified Hoehn and Yahr PD Severity Scale Assessment

The modified Hoehn and Yahr PD stage 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 14: 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 15: Spirometry Alert and Review Process Diagram

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%

Patient is NOT sent home with study drug

1) Manage emergent medical condition(s)

(2a) Complete Spirometry Alert Review Worksheet and transmit to prespecified personnel

(2b) Transmit spirometry data to Spirometry Core Lab (BMS)

3) Complete all other TV1 safety assessments if patient is stable and able to continue
Appendix 16: 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