16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plans

Statistical Analysis Plan version 2.0 dated 29 June 2017

16.1.9.2 Method for Analysis of Abuse Related Adverse Events

Abuse Assessment Section Terms

Study No. CVT-301-004E Summary of SAP Changes from Interim Analysis SAP Version 1.0 (11Jan2017) to Interim Analysis SAP Version 2.0 (29Jun2017)	
Interim Analysis SAP Version 1.0 (11Jan2017)	Interim Analysis SAP Version 2.0 (29Jun2017)
Cover page: Protocol Number and Title: A 12-Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Protocol Version and Date: Version 5.0/5.1, 14-Nov-2016/30-Nov-2016 SAP version and date: Interim Analysis SAP Version 1.0, 11-Jan-2017	Cover page: Protocol Number and Title: A 12-Month (or 14-Month for Patients Enrolled into sub-Study), Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) (SPANPD™) Protocol Version and Date: Version 5.0/5.1, 14-Nov-2016/30-Nov-2016; Version 5.2 for sub-Study, 07-Dec-2017 SAP version and date: SAP Version 2.0, 29-Jun-2017
3.3 Safety Objectives • To characterize the effects of CVT-301 on safety and tolerability over a 12-month period, assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), 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-	3.3 Safety Objectives • To characterize the effects of CVT-301 on safety and tolerability over a 12-month period, assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), 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, the Columbia-Suicide Severity Rating Scale (C-SSRS),

SSRS).	the Amphetamine Withdrawal Questionnaire (AWQ), the Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS).
4.3 Safety Endpoints	4.3 Safety Endpoints • Amphetamine Withdrawal Questionnaire (AWQ) will be assessed at the clinic in an ON state at TV1 and TV6 or Early Termination (ET) or TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit after the patients enrolled into sub-study. For patients who didn't enrolled into the sub-study, the AWQ will also be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled into the sub-study, the AWQ will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The total score will be calculated as the sum of the individual items 1 to 10. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items. • Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC) will be assessed at the clinic in an ON state at TV1 and TV6 or Termination (ET) or TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit after the patients enrolled into sub-study. For patients who didn't enrolled into the sub-study, the DDS-PC will also be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled into the sub-study, the DDS-PC will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The total score will be calculated as the sum of the individual items 1 to 45. The below score will be used

	for each individual item: 0 = Not at all, 1 = Very little, 2 = A little, 3 = Quite a lot, 4 = Very much. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items. • Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts 1B and 2 will be assessed during drug withdrawal period. For patients who didn't enrolled into the sub-study, the MDS-UPDRS will be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled in the sub-study, the MDS-UPDRS will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The Part 1B score will be calculated as the sum of the individual items 1.7 to 1.13 and the Part 2 score as sum of 2.1 to 2.13. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.
8.1 Efficacy Endpoints and Analyses	8.1 Efficacy Endpoints and Analyses • Change from baseline (TV1) and Last Day of Treatment (LDOT) to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after TV6 in the PHQ-9 will be summarized descriptively. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.
9.9 COLUMBIA-SUICIDALITY SEVERITY RATING SCALE	9.9 COLUMBIA-SUICIDALITY SEVERITY RATING SCALE A shift table from baseline to each visit, days 1, 3, 6, 8, 11, 14, 17, 24, and

A shift from baseline table will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.	28 after LDOT will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period. A shift table from LDOT to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after TV6 will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.
9.10 EPSWORTH SLEEPINESS SCALE All Epworth Sleepiness Scale data will be listed. The total score and change from baseline to each visit will be summarized by treatment group and overall (for handing of data from the ET visit, see Section 6.4).	9.10 EPSWORTH SLEEPINESS SCALE All Epworth Sleepiness Scale data will be listed. The total score and change from baseline to each visit will be summarized by treatment group and overall (for handing of data from the ET visit, see Section 6.4). The total score and change from baseline (TV1) and Last Day of Treatment to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment will also be summarized. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.
	9.14 AMPHETAMINE WITHDRAWAL QUESTIONAIRE (AWQ) The actual values and changes from baseline (TV1) and LDOT to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after LDOT in AWQ total score will be summarized descriptively for patients in safety population. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.
	9.15 DOPAMINE DYSREGULATION SYNDROME - PATIENT AND CAREGIVER INVENTORY (DDS-PC) The actual values and changes from baseline (TV1) and Last Day of Treatment to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment in DDS-PC total score will be summarized descriptively for patients in safety population. LDOT is defined

	as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.
	9.16 MOVEMENT DISORDER SOCIETY - UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) The MDS-UPDRS Part 1 and Part 2 value will be summarized descriptively on days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment by treatment for patients in the safety population.

Statistical Analysis Plan

Document Type:	Template	Document ID:
Issue Date:	02 APR 2012	Effective Date: 30 APR 2012

Sponsor Name:	Civitas Therapeutics, Inc.
Protocol Number and Title:	CVT-301-004E A 12-Month (or 14-Month for Patients Enrolled into sub-Study), Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) (SPANPD™)
Protocol Version and Date:	Version 5.0/5.1, 14-Nov-2016/30-Nov-2016; Version 5.2 for sub-Study, 07-Dec-2017
INC Research Project Code:	1003804
Author(s):	[redacted]
SAP Version:	SAP Version 2.0
SAP Version Date:	29-Jun-2017

Statistical Analysis Plan

Version: SAP Version 2.0 **Version Date:** 29-Jun-2017

I confirm that I have reviewed this document and agree with the content.

APPROVALS
INC Research
[redacted]

Statistical Analysis Plan

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AAP	All Available Population
ADL	Activities of Daily Living
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AWQ	Amphetamine Withdrawal Questionnaire
BMI	Body Mass Index
BP	Blood Pressure
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
C-SSRS	Columbia-Suicidality Severity Rating Scale
DBP	diastolic blood pressure
DDI	Dopamine Decarboxylase Inhibitor
DDS-PC	Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory
DL	Dose Level
DLCO	Carbon Monoxide Diffusion Capacity
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ERS	European Respiratory Society
ET	Early Termination
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity

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Abbreviation	Description
Hb	Hemoglobin
HR	Heart Rate
HCG	human chorionic gonadotropin
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LD	Levodopa
LDOT	Last Day of Treatment
LS	least square
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMSE	Mini Mental State Examination
MMRM	Mixed Model for Repeated Measures
PCS	potentially clinically significant values
PCSC	potentially clinically significant changes
PD	Parkinson's Disease
PDQ-39	39-Item Parkinson's Disease Questionnaire
PGI-C	Patient Global Impression of Change
PMM	Pattern Mixture Models
PRN	As needed
PT	Preferred Term

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Abbreviation	Description
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RR	Respiratory Rate
S&E	Schwab and England
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	Standard Deviation
SEM	Standard Error of the Mean
SI	International System of Units
SOC	System Organ Class
SV	Screening Visit
TEAE	Treatment-Emergent Adverse Event
TLF	tables, listings, figure
TV	Treatment Visit
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-DD	World Health Organization Drug Dictionary

Statistical Analysis Plan

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP describes the statistical analysis as it is foreseen at the time of planning the study. The SAP will serve as a compliment to the study protocol and supersedes it in case of differences. In case of major differences between the study protocol and SAP (e.g. changes in the analysis related to the primary endpoint) protocol amendment will be considered. The SAP may be updated during the conduct of the study and will be finalized before the data base lock. However, the analyses defined after the blind of study CVT-301-004 has been broken will be considered as exploratory.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. Acorda (or its designee) will review and approve all statistical work done by INC Research as agreed between INC Research and Acorda.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and efficacy is planned after all patients complete the final study visit or terminate early from the study, and database is cleaned and locked.

3. STUDY OBJECTIVES AND STUDY DESIGN

3.1. PRIMARY OBJECTIVE

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

3.2. SECONDARY OBJECTIVES

The following secondary objectives will be assessed for the patients who were previously enrolled in the CVT-301-004 study and for the CVT-301-naïve patients (including CVT-301-005 observational arm patients):

- 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).
- Change from baseline in patient-reported total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, assessed by the patient and recorded in the patient diary.
- Change from baseline visit in 39-Item Parkinson's disease Questionnaire (PDQ-39).
- Proportion of patients who improved based on the Patient Global Impression of Change (PGI-C) rating scale measured at baseline.
- Change from baseline visit in Schwab and England (S&E) Activities of Daily Living (ADL) score.
- Change from baseline visit in 9-Item Patient Health Questionnaire (PHQ-9).
- Change from baseline visit in Impact of Parkinson's OFF Episodes Patient Survey
- Change from baseline visit in UPDRS Part 2 score.

3.3. SAFETY OBJECTIVES

- To characterize the effects of CVT-301 on safety and tolerability over a 12-month period, assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), 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, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Amphetamine Withdrawal Questionnaire (AWQ), the Dopamine Dysregulation

Syndrome - Patient and Caregiver Inventory (DDS-PC), and the self-administered MDS-UPDRS Parts 1B and 2 (Movement Disorder Society -UPDRS).

- To describe the effect of CVT-301 on DLCO.
- To compare the pulmonary safety, as assessed by spirometry (FEV1, FVC and FEV1/FVC ratio) between the group of patients who were treated with CVT-301 in study CVT 301-004 versus the CVT-301 patients treated with placebo in CVT 301-004.
- Change from baseline visit in 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.

3.4. PATIENT SELECTION

The following patients are eligible for study CVT-301-004E:

1. Patients who completed study CVT-301-004, treated with either CVT-301 35 mg LD FPD, CVT-301 50 mg LD FPD or placebo
2. Patients who completed study CVT-301-003, treated with either CVT-301 35 mg LD FPD followed by CVT-301 50 mg LD FPD or placebo (enrolled prior to Amendment 4)
3. Patients who completed study CVT-301-009, treated with either single dose of CVT-301 50 mg LD FPD or placebo
4. Patients who were randomized to the observational arm of study CVT-301-005 and completed that study
5. CVT 301 naïve patients who did not participate to previous CVT-301 studies.

Patients who withdrew from the CVT-301-004, CVT-301-003, CVT-301-009 or CVT-301-005 studies prior to completion, for any reason, are not eligible.

3.4.1. Inclusion Criteria

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

The inclusion criteria listed below are not assessed for the CVT-301-004 study patients. In order to be eligible to enter the study, patients must meet all of the following criteria:

- Has signed and dated an IRB/IEC-approved informed consent form before any protocol-specific screening procedures are performed.
- Is a male or female aged 30 to 86 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (HCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
- Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the United Kingdom (UK) Brain Bank criteria, diagnosed after the age of 30 years.
- Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
- Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.
- Patients who are on a LD-containing therapy, not including Rytary (or equivalent), must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/dopamine decarboxylase inhibitor (DDI)-containing regimen.
- Patients who are on a LD-containing therapy, when including Rytary (or equivalent), should be on a stable dose for at least 6 weeks prior to SV1
- The frequency of L-dopa administrations must be at least 3 times during the waking day and a total daily LD dose of ≤ 1600 mg
- Patients should be stable on other PD medications for at least 4 weeks prior to SV1.
- Patients must have normal cognition as confirmed by a score of ≥25 on the MMSE.
- Patients must be able to perform a spirometry maneuver in the ON and OFF states and must have a screening FEV1 ≥ 50% of predicted, and an FEV1/FVC ratio > 60% in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patients with an FEV1 that is ≥ 50% to < 60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine eligibility. Patients with an FEV1/FVC ratio that is >60% to <70% will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/European Respiratory Society [ERS] criteria prior to randomization. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization.)

3.4.2. Exclusion Criteria

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

- Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures.
- Pregnant or lactating females or females wishing to become pregnant.
- Patients who have any known contraindication to the use of LD, including a history of malignant melanoma or a history of narrow-angle glaucoma.
- Patients who have had previous surgery for PD (including but not limited to cell transplantation) or plan to have stereotactic surgery during the study period. Patients who have had deep brain stimulation [DBS] will also be excluded unless the procedure was performed more than 6 months prior to study enrollment.
- Patients with a history of psychotic symptoms requiring treatment, or suicidal ideation or attempt within the prior 12 months.
- Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
- Patients taking certain prohibited medications (see protocol 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 15 for a list of contraindications).
- Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment.
- Patients with any condition that in the investigator's opinion would make patients unable to comply with study procedures or make them unsuitable for their participation in the study.
- Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety. Potential issues of concern should be raised to the medical monitor during eligibility review.
- For new CVT-301 naïve patients, patients who have been treated with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the beginning of the screening period (this includes investigational formulations of marketed products).

3.5. DETERMINATION OF SAMPLE SIZE

The study is planned to enroll 390 patients to ensure that approximately 290 patients will complete the 12 month study. The sample size of this study is designed in order to

capture sufficient amount of safety data required for regulatory submissions and is not based on formal statistical calculations.

3.6. TREATMENT ASSIGNMENT & BLINDING

This study is a randomized, dose-level blinded, multicenter study of inhaled CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes). Following completion of SV2 and prior to randomization (for CVT-301-003, CVT-301-009, CVT-301-005 and other CVT-301-naïve patients), eligibility criteria will be reviewed by delegated staff. Sites must leave a minimum of 5 days between randomization and Treatment Visit 1.

Before TV1, patients will be assigned/randomized to treatment group [Dose Level (DL) 1, or 2]. Patients who received DL1 (target nominal dose of 35 mg LD FPD) in the CVT-301-004 study will receive DL1 (target nominal dose of 35 mg LD FPD) in this study, and patients who received DL2 (target nominal dose of 50 mg LD FPD) in the CVT-301-004 study will receive DL2 (target nominal dose of 50 mg LD FPD) in this study. Patients who received placebo in the CVT-301-004 study, CVT-301-003 patients, CVT-301-009 patients, and CVT-301-naïve patients (including CVT-301-005 observational arm patients) will be randomized in a 1:1 ratio to DL1 or DL2.

Upon confirmation of eligibility, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). Randomization will be differentiated by the patient's Hoehn and Yahr PD disease severity scale rating (<2.5 versus ≥2.5) to balance for disease severity across each treatment group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%). For the patients who received placebo in CVT 301 004, the differentiation of CVT 301 004 will be used. Patients and site staff will be blinded to treatment group.

3.7. ADMINISTRATION OF STUDY MEDICATION

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 Instructions for Use (IFU). The IFU will be provided to each patient and will be part of the permanent study record.

In order to blind the treatment group, study kits with identical number and appearance of capsules will be distributed to patients in the CVT-301 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 treatment group.

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

During inhaler training, patients will be instructed to use the inhalation system in accordance with the IFU which includes a breath hold of 5 seconds following each capsule inhalation. 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 re-inhaled, T0 is at the end of the re-inhalation administration.

During the treatment period, patients will self-administer inhaled study treatment (CVT-301 DL1 or CVT-301 DL2) up to 5 times daily to treat OFF episodes during their waking day.

3.8. STUDY PROCEDURES AND FLOWCHART

This study has 3 periods: screening period, treatment period, and follow-up period; and a total of 9 planned visits: 2 screening visits, 6 treatment visits, and 1 follow-up visit. The maximum anticipated duration of this study for patients from the CVT-301-004 study will be approximately 59 weeks, including the final spirometry and DLCO assessment which takes place 4 to 5 weeks following the treatment period. The maximum anticipated duration of this study for CVT-301-naïve patients and CVT-301-009 patients, including the screening period and the final spirometry and DLCO assessments, will be approximately 64 weeks.

CVT-301-naïve patients (including CVT-301-005 observational arm patients) will undergo a screening period (of up to 35 days) prior to randomization. The screening period may be extended an additional 7 days if repeat screening assessments are required. The screening period will consist of 2 scheduled clinic visits: Screening Visit 1 (SV1) and Screening Visit 2 (SV2). CVT-301-004 patients will not be required to undergo the screening visits and will undergo TV1 after a 1- to 14-day period (or longer if approved by the Sponsor) following Treatment Visit 4 (TV4) of the CVT-301-004 study.

Before patients return to the clinic for TV1, they will be randomized to treatment group (see section 3.6 for details). The treatment period includes 6 separate in-clinic visits

over approximately 52 weeks. The first dose of study drug will be given in the clinic at TV1. The subsequent visits during the treatment period take place as follows:

- TV2: Week 4; 28±5 days after TV1.
- TV3: Week 12; 84±14 days after TV1.
- TV4: Week 24; 168±14 days after TV1.
- TV5: Week 36; 252±14 days after TV1.
- TV6: Week 52; 364±14 days after TV1.

Patients who terminate the study early will complete TV6 and return for the Follow-up DLCO visit 4-5 weeks after TV6.

Refer to Protocol Appendices 2 to 10 for tables of study assessments at each visit.

4. ENDPOINTS

4.1. PRIMARY ENDPOINT

The primary endpoints related to the primary objective of the study are the pulmonary safety measures, FEV1, FVC and FEV1/ FVC ratio, assessed over a 12 month period. FEV1, FVC and FEV1/FVC ratio will be recorded from the single "best test" (based on effort with highest summed FEV1 and FVC). Variables will include the absolute FEV1, FVC, and FEV1/FVC ratio and FEV1 and FVC expressed as % of predicted value. Changes from baseline (TV1) for each variable will be calculated at each subsequent visit.

Percent Predicted = 100 * (Observed) / Predicted, where predicted values are calculated using the formulae by Hankinson et al (Spirometric Reference Values from a Sample of the General U.S. Population, 1999):

Caucasian males ≥20 years of age:

- FVC predicted = -0.1933 + 0.00064*age - 0.000269*age^2 + 0.00018642*height^2
- FEV1 predicted = 0.5536-0.01303*age -0.000172*age^2 + 0.00014098*height^2

Caucasian females ≥18 years of age:

- FVC predicted = -0.3560 + 0.01870*age -0.000382*age^2 + 0.014815*height^2
- FEV1 predicted = 0.4333 - 0.00361*age -0.000194*age^2 + 0.00011496*height^2

, Please see Hankinson et al (1999) for formulae for other races and age categories

4.2. SECONDARY ENDPOINTS

The following endpoints related to the secondary objectives will be calculated.

- Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic and maintaining the ON at 60 minutes after study drug administration (per the examiner's subjective assessment). This endpoint will be based on the examiner's subjective assessment. In case the assessment of turning on within 60 minutes is missing but the assessment of maintaining the ON at 60 minutes has been done, the patient will be classified based on the available assessment. In case the assessment of maintenance of ON at 60 minutes is missing, the patient will be classified as not achieving resolution of an OFF to an ON state.

- Change from baseline (3 consecutive days prior to TV1, or in case of missing data, the last 3 recorded days before TV1) in patient-recorded total daily OFF time, assessed by the patient and recorded in the PD Diary for 3 consecutive days prior to in-clinic visits (or in case of missing data, the last 3 recorded days before the visit). The validity of the PD diary entries will be checked prior to including a diary day in the summary calculations. Only valid diary days will be included in the diary summarizations. Change from baseline in total daily ON time without dyskinesia, in total daily ON time with non-troublesome dyskinesia, and in total daily ON time with troublesome dyskinesia will be calculated similarly.

    - A day will be considered as being valid if at least 80% of the entries during the day have been completed per instructions. That is, for each half hour period, only one entry among the responses (Asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, or ON with troublesome dyskinesia) has been checked. The entry will not be used if no responses are checked or more than one response is checked. However, if the proportion of entries rejected due to multiple checked responses is large, sensitivity analysis will be performed by using the worst case out of the entries that had been checked. The worst case will be defined in the following order: OFF, ON with troublesome dyskinesia, ON with non-troublesome dyskinesia, ON without dyskinesia, Asleep. In case there are duplicate entries (i.e., multiple entries recorded with same date and time interval), the worst entry will be used for the date and time interval in question. The worst entry will be selected in the order defined above.

    - All diary data will be normalized to 16 awake hours per day. The daily OFF time will be extrapolated to a 16 hour period by determining the percentage of OFF time among accurately recorded entries, excluding asleep time and missing/non-valid recordings, and by multiplying this percentage by 16 hours.

        - Off Time / (Total time recorded - Asleep Time - missing time interval) x 16

    - The mean daily OFF time prior to each visit will be calculated as mean value of the valid days documented in the patient's diary prior to that visit. In case there are gaps within the 3 days preceding the visit, the last 3 recorded days before the visit will be used regardless of the gaps. If there are more than 3 valid days, only the last 3 days will be used. If there are only 1 or 2 valid days, the average of these days will be used.

- Change from TV1 (baseline) in PDQ-39 sub-scores (mobility score, activities of daily living, bodily discomfort score, emotional wellbeing score, social support score, communication score, cognitive impairment score, and stigma score) and summary

index score. The questionnaire provides scores on eight dimensions as outlined below:

- mobility (10 items, #1 to 10)
- activities of daily living (6 items, #11 to 16)
- emotional well-being (6 items, #17 to 22)
- stigma (4 items, #23 to 26)
- social support (3 items, #27 to 29)
- cognitions (4 items, #30 to 33)
- communication (3 items, #34 to 36)
- bodily discomfort (3 items, #37 to 39)

Items are scored from 0 (never) to 4 (always). Dimension scores are obtained by dividing the sum of the item scores by the maximum possible score for any given dimension and expressing this as a percentage. For example:

- mobility = (sum of scores of #1 to 10)/(4 x 10) x 100
- activities of daily living = (sum of scores of #11 to 16)/(4 x 6) x 100

For social support, if the response indicates that a patient does not have a spouse or partner for #28, social support can be calculated as [(sum of scores of #27 and 29)/(4 x 2) x 100].

A summary index is then calculated as the sum of the total score of the dimensions divided by the number of dimensions, i.e. (sum of dimension scores / 8). If any item score is missing, the relevant dimension score and the summary index will be missing.

- Change from TV1 (pre-dose) in 9-Item PHQ-9 sum score. The sum score will be calculated as the sum of the 9 individual questions. In case of 1 or more missing questions, the sum score will be set as missing.

- Change from baseline in Impact of Parkinson's OFF Episodes Patient Survey. The Impact of Parkinson's OFF episodes patient survey score will be calculated as the sum of the individual items of the Impact of Parkinson's OFF Episodes Patient Survey questionnaire. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.
- The PGI-C score. The non-missing values will be categorized as improvements (much improved, improved, a little improved) or non-improvements (no change, a little worse, worse, much worse).

- Change from TV1 (baseline) in Schwab and England (S&E) Activities of Daily Living (ADL). No further derivation will be done for the S&E scores.

- Change from TV1 (pre-dose) in the UPDRS Part 2 score. The UPDRS Part 2 score will be calculated as the sum of the individual items of the UPDRS Part 2 questionnaire (UPDRS items 5-17). Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

4.3. SAFETY ENDPOINTS

The following endpoints related to the secondary objectives will be calculated.

- Standard safety endpoints; for definitions see Section 9 of this SAP
  - Adverse Event (AE) reports
  - Physical examination
  - Standard and orthostatic vital signs (BP, HR and RR)
  - Clinical laboratory tests (hematology, clinical chemistry, and additional laboratory parameters)
  - 12-lead ECGs (HR, PR, QRS, QT, QT interval corrected using Bazett's formula [QTcB] and QT interval corrected using Fridericia's formula [QTcF])
  - Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP)
  - Epworth Sleepiness Scale
  - Columbia-Suicide Severity Rating Scale (C-SSRS)

- Occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic. The occurrence will be based on the examiner's subjective assessment and no further derivation will be performed. Among the patients with reported dyskinesia, the severity will be classified as mild, moderate, severe or missing based on the examiner's subjective assessment and no further derivation will be performed. Only observed cases will be used for this endpoint and the visits with missing data will not be included in the analysis.

- Change from TV1 (baseline) in the UPDRS Part 4 sum scores of dyskinesias (UPDRS items 32-35) and wearing-off (UPDRS items 36-39). The dyskinesia score will be calculated as the sum of the individual items 32-35 and the wearing-off score as sum of 36-39. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

- Carbon Monoxide Diffusion Capacity (DLCO) assessed over a 12 month period. Variables will include the absolute DLCO values and DLCO expressed as % of predicted value.

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- Amphetamine Withdrawal Questionnaire (AWQ) will be assessed at the clinic in an ON state at TV1 and TV6 or Early Termination (ET) or TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit after the patients enrolled into sub-study. For patients who didn't enrolled into the sub-study, the AWQ will also be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled into the sub-study, the AWQ will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The total score will be calculated as the sum of the individual items 1 to 10. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

- Dopamine Dysregulation Syndrome - Patient and Caregiver Inventory (DDS-PC) will be assessed at the clinic in an ON state at TV1 and TV6 or Termination (ET) or TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit after the patients enrolled into sub-study. For patients who didn't enrolled into the sub-study, the DDS-PC will also be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled into the sub-study, the DDS-PC will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The total score will be calculated as the sum of the individual items 1 to 45. The below score will be used for each individual item: 0 = Not at all, 1 = Very little, 2 = A little, 3 = Quite a lot, 4 = Very much. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

- Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts 1B and 2 will be assessed during drug withdrawal period. For patients who didn't enrolled into the sub-study, the MDS-UPDRS will be completed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV6/ET. For patients who enrolled in the sub-study, the MDS-UPDRS will be assessed at home at 1, 3, 6, 8, 11, 14, 17, 24, and 28 days after TV4, TV5 or TV6, depending on which of the visits is the next scheduled visit for those patients. The Part 1B score will be calculated as the sum of the individual items 1.7 to 1.13 and the Part 2 score as sum of 2.1 to 2.13. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

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5. ANALYSIS SETS

5.1. ALL AVAILABLE POPULATION (AAP)

The AAP will include all patients who have consented for the study, including screening failures. Unless specified otherwise, the AAP will be used for patient listings and for the summary of patient disposition.

5.2. SAFETY POPULATION

The Safety Population will include all patients in AAP who are enrolled in CVT-301-004E and received at least 1 dose of inhaled CVT-301. Patients will be analysed according to the highest dose level that they received. The Safety Population will be used for all analyses of safety endpoints and summaries of patient demographics and baseline characteristics.

5.3. INTENT-TO-TREAT POPULATION (ITT)

The ITT population will include all patients from the safety population. However, due to the different study designs, the patients enrolled from CVT-301-003 and CVT-301-009 will not be included in efficacy summaries (i.e. the patients enrolled from CVT-301-003 and CVT-301-009 will be excluded from ITT population). The rationale for excluding the CVT-301-003 patients from the efficacy summaries is the gap between the end of CVT-301-003 and start of CVT-301-004E. The rationale for excluding the CVT-301-009 patients from the efficacy summaries is the study design (single-dose study) which is not comparable to the design of the rest of the studies. Patients will be analyzed according to randomized treatment group. The ITT Population will be used for all analyses of efficacy endpoints and summaries of patient demographic and baseline disease characteristics.

In case of variables which are not captured throughout the whole study but only added after an protocol amendment (e.g. PHQ-9), the ITT population for the variable in question includes only the subset of the ITT population in which at least the baseline and one post-baseline assessment of the variable in question were done.

5.4. PROTOCOL DEVIATIONS

A protocol deviation is any significant finding 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 or within an acceptable visit window for completion of study assessments). The deviation may necessitate premature termination of the patient from the visit assessments, or from the study.

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The deviations will be classified during a blind review process with the Sponsor and other study personnel (as appropriate) before database lock. The deviations will be classified as minor or major during a blind review process. All decisions regarding major/minor deviations will also be discussed between the Sponsor, other study personnel (as appropriate), and the study statistician prior to commencing the final analysis on the locked database.

The number of subjects with protocol deviations will be summarized by treatment group and overall. All protocol deviations will be listed.

Statistical Analysis Plan

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All patient data will be included in listings. All patients entered into the database will be included in patient data listings. The listings will be generally sorted by the study (and treatment) from which the patient was enrolled, Patient ID (and by visit and by time point, if applicable) within treatment group, unless specified otherwise.

All applicable data will be summarized by treatment group (CVT-301 DL1, CVT-301 DL2, CVT-301 overall) in tables, unless specified otherwise. Furthermore, selected summaries will be broken down into three groups as follows: patients who received CVT-301 in CVT-301-004 study, patients who received placebo in CVT-301-004 study and CVT-301 naïve patients (including CVT-301-005 observational arm patients) (referred to as "treatment/study group" in the SAP). The efficacy data from patients who were enrolled in the CVT-301-003 or CVT-301-009 study will be analyzed separately, as data listings. In addition, a patient disposition table will be provided for CVT-301-003 and CVT-301-009 patients. Where appropriate, data will be summarized by visit and/or time point in addition to treatment group. Unscheduled or repeat assessments will not be included in summary tables, but will be included in listings.

Continuous variables will be summarized using the number of observations (n), mean, SD, median, minimum, and maximum. Standard error of the mean (SEM) will also be provided for summaries of spirometry and efficacy endpoints, if relevant. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD and SEM.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of patients in each treatment group/overall (N) will be used as the denominator for percent calculations, unless stated otherwise in the table shell. All percentages will be presented with one decimal point, unless specified otherwise. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

Significance testing will be 2-tailed using $\alpha = 0.05$, unless otherwise specified. All analyses and summaries will be produced using SAS® version 9.3 (or higher).

Deviations from the statistical plan will be reported in the clinical study report, including the rationale for use and information on whether the deviation was done before or after the blind of study CVT-301-004E was broken.

6.2. KEY DEFINITIONS

Age

Age, as an integer, will be calculated using the date of birth and baseline date.

Age = int ((baseline date - date of birth)/365.25)

Body Mass Index (BMI)

BMI will be calculated as follows and rounded to 1 decimal place:

BMI (kg/m^2) = weight (kg) / [height (m)]^2

Parkinson 's disease History

The following parameters will be calculated for the PD history:

Time since diagnosis of PD (months) =
Baseline Date (M/Y) - Date of diagnosis (M/Y)

Duration of levodopa treatment (months) =
Baseline Date (M/Y) - Start date of levodopa treatment (M/Y)

Time since onset of wearing off episodes (months) =
Baseline Date (M/Y) - Date of onset of wearing off episodes (M/Y)

For the definition of baseline data, see below. If the month is missing, the first month of the year will be used.

Change from pre-dose to post-dose

The change from pre-dose to post-dose within each visit will be calculated for each post-dose assessment as:

Change from Pre-dose to Post-dose = Post-dose value - Pre-dose value

Percent change from pre-dose to post-dose

The percent change from pre-dose to post-dose within each visit will be calculated for each post-dose assessment as:

Percent Change from Pre-dose to Post-dose =
(Post-dose value - Pre-dose value)*100/Pre-dose value

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Baseline

Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients.

Change from baseline

The change from baseline will be calculated for each post-baseline assessment as:

Change from Baseline = Post-baseline value - Baseline value

Percent change from baseline

The percent change from baseline will be calculated for specified post-baseline assessments as:

Percent Change from Baseline =
(Post-baseline value - Baseline value)*100/Baseline value

DLCO predicted

DLCO predicted will be calculated by Miller equation. *(Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative of Michigan, a large industrial state. Am Rev Resp Dis 1983; 127: 270-277).*

- *Men predicted DLCO = 12.9113 - (0.229 x age) + (0.418 x height)*
- *Women predicted DLCO = 2.2382 - (0.1111 x age) + (0.4068 x height)*

where age is the age at baseline, height is measured in inches.

DLCO Predicted, adjusted for Hb

DLCO predicted adjusted for Hb is calculated using the Cotes method, according to the 2005 ATS/ERS guidelines for DLCO.

- *DLCO predicted, adjusted for Hb in adult men:*
  $$DLCO_{predicted\ for\ Hb} = DLCO_{predicted} * 1.7 * Hb / (10.22 + Hb)$$
- *DLCO predicted, adjusted for Hb in adult women:*
  $$DLCO_{predicted\ for\ Hb} = DLCO_{predicted} * 1.7 * Hb / (9.38 + Hb)$$

where $DLCO_{predicted}$ is the DLCO calculated from Miller equation; Hb = hemoglobin, measured in g/dL. The Hb closest to the date/time of DLCO taken will be used.

Percent predicted of FEV1 and FVC

The percent predicted of FEV1 and FVC will be calculated using the following equation.

*Percent Predicted = 100 * (Observed) / Predicted*

where the predicted value is the value calculated based on formulae by Hankinson et al (1999) . The details are listed in table below.

$DLCO_{predicted}$, percent predicted of FEV1 and FVC	In case a variable used to calculate the predicted value (age, height, Hb) is missing, the following imputation rules will be used in order to calculate the predicted value:
Screening (prior to randomization)	Age, height or Hb from TV1 or the value closest to the date of DLCO/FEV1/FVC assessment if the value at TV1 is missing
TV3, within 2 weeks prior to 3	Age, height or Hb from TV3 or the value closest to the date of DLCO/FEV1/FVC assessment if the value at TV3 is missing
TV4, within 2 weeks prior to 6	Age, height or Hb from TV4 or the value closest to the date of DLCO/FEV1/FVC assessment if the value at TV4 is missing
TV5, within 2 weeks prior to 9	Age, height or Hb from TV5 or the value closest to the date of DLCO/FEV1/FVC assessment if the value at TV5 is missing
TV6, within 2 weeks prior to 12	Age, height or Hb from TV6 or the value closest to the date of DLCO/FEV1/FVC assessment if the value at TV6 is missing
4 to 5 weeks after TV6	The latest non-missing Hb closest to the date of DLCO/FEV1/FVC assessment taken.

6.3. MISSING DATA

Several different methods to handle the missing data in efficacy assessments will be used.

- For the primary analysis of spirometry and selected efficacy endpoints, likelihood-based modeling approach will be used to handle incomplete data. For this purpose, Mixed Model for Repeated Measures (MMRM) will be applied (see Section 8.1.)

- Sensitivity analysis for spirometry and selected explorative efficacy endpoints will be conducted using the Multiple Imputation (MI) approach, i.e. by replacing each missing value with a set of plausible values that represent the uncertainty about the right value to impute, see Section 9.1.

- For the binary explorative efficacy endpoints, sensitivity analyses will be conducted using worst case imputation, where visits with missing data are counted as non-resolved (primary method), see Section 8.1.

- For AEs, the overall incidence of TEAEs, normalized for duration of exposure will be calculated to account for the shorter follow-up time in patients who discontinue the study prematurely, see Section 9.4.

The Safety and ITT population will be used for the analysis of the primary and secondary endpoints. This population includes all patients enrolled to study CVT-301-004E who received at least 1 dose of inhaled CVT-301, regardless of whether they have post-baseline data or not for the variable in question. The patients with no post-baseline data will not contribute to the analyses performed with the MMRM approach, but they do contribute to the sensitivity analyses using the MI approach. Due to this, no additional population, like a modified ITT population including only the patients with post-baseline will be defined.

Safety data (other than the primary endpoint) will not be subjected to any imputation and will be summarized on an observed case basis.

6.4. VISIT WINDOWS

The visits recorded in database will be used for all analyses. There is no plan to re-assign visits based on actual visit dates.

For the patients who discontinue the study prematurely, a set of assessments is scheduled to be performed at the ET visit (PDQ-39, PHQ-9, PGI-C, UPDRS Part 2, UPDRS Part 4, S&E ADL score and safety assessments). The following rules will be used to analyze the data collected at the ET visit:

- For the PDQ-39, PHQ-9, PGI-C, UPDRS Part 2, UPDRS Part 4 and S&E ADL score, the data from the ET visit will be re-assigned to TV6 in case there is no TV6 assessment.

- In case there are PD diary assessments performed during the three days before the ET visit, these assessments will be re-assigned to the first visit at which the PD diary assessments were scheduled but are missing due to the premature withdrawal.

- The safety assessment assessments performed at the ET visit will be re-assigned to the first time point at which the corresponding safety assessments were scheduled but are missing due to the premature withdrawal.

- Any other data collected at the ET visit will not be used.

6.5. POOLING OF SITES

Not applicable.

6.6. SUBGROUPS

At least the following subgroup analyses have been pre-planned. The subgroup analyses will be performed for selected safety/efficacy endpoints (at least the change from baseline in total daily OFF time). Selected baseline data will be presented for the subgroups as well.

- Patients with baseline PD severity < 2.5 points on the Hoehn & Yahr scale versus patients with baseline PD severity ≥ 2.5 points on the Hoehn & Yahr scale

- Patients who are dyskinetic before TV1 versus non-dyskinetic patients. The classification will be done based on the Parkinson's disease diary data. The patients who have recorded at least 1 hour of dyskinesia (either ON with non-troublesome dyskinesia or ON with troublesome dyskinesia) on at least 2 days before TV1 will be classified as dyskinetic

- Patient with the baseline daily levodopa dose less than or equal to the median versus the patients with the baseline daily levodopa dose higher than the median

- Patients who have less than 4.5 hours of PD diary mean daily OFF time before TV1 versus patients who have 4.5 hours or more of OFF time

- Patients with FEV1 <60% of predicted or FEV1/FVC ratio <70% at baseline versus patients with FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%

- Non-elderly (<65 years) versus elderly (≥65 years) patients

- Female versus male patients

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

The patient disposition table will summarize the following and will be presented for each treatment group, as applicable, and overall for APP. In addition, the data will be broken down by treatment/study group (patients who received inhaled CVT-301 in CVT-301-004 study, patients who received placebo in CVT-301-004 study and CVT 301 naïve patients (including CVT-301-005 observational arm patients). The patient disposition table will also be provided for CVT-301-003 and CVT-301-009 roll-over patients. The percentages will be calculated based on the number of patients enrolled to study CVT-301-004E, unless otherwise specified).

- The number of patients screened (i.e. the number of patients in the AAP population)
- The number of patients who failed screening
- The number (%) of patients enrolled into the CVT-301-004E study (% calculated from the AAP population)
- The number (%) of patients in the different study populations (Safety and ITT populations)
- The number (%) of patients who completed the study (based on end-of-study case record page, % calculated from the Safety population)
- The number (%) of patients who withdrew from the study and associated reasons (% calculated from the Safety population)

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized descriptively for the safety and ITT population by treatment group and overall. In addition, the data will be broken down by treatment/study group. The following variables will be summarized:

- Demographics (age (continuous), age categorized as <65 years versus ≥65 years, gender, ethnicity, race, height, weight, BMI, country)

- Smoking history (current, former, never, Number of Years Smoked and Number of Cigarettes/Day)

- Cognitive status (MMSE)

- Average number of daily OFF episodes experienced from the Screening ON/OFF Log. The screening ON/OFF log data collected on 3 days prior to TV1 will be used

as baseline. If the data are only available on 1 or 2 days prior to TV1, the available data will be used as baseline. If there is no data prior to TV1, the data collected on 3 days prior to SV2 will be used as baseline.

- Proportion of patients who changed the timing of their usual levodopa medication and proportion of patients who took an extra dose of levodopa or other PD medication from the Screening ON/OFF Log. The screening ON/OFF log data collected on 3 days prior to TV1 will be used as baseline. If the data are only available on 1 or 2 days prior to TV1, the available data will be used as baseline. If there is no data prior to TV1, the data collected on 3 days prior to SV2 will be used as baseline.

- Average daily OFF time, ON time without Dyskinesia, ON time with troublesome and non-troublesome dyskinesia (from PD diary before TV1)

- Proportion of patients with total daily OFF time <4.5 hours or ≥4.5 hours (from PD diary before TV1)

- Distribution of average daily OFF time in 30-minute intervals (00:00 - 00:30, 00:30 - 01:00 ...). The percentage based on the total daily OFF time will also be presented and is calculated as the average of total OFF time collected three days prior to TV1 and is normalized to 16 awake hours per day.

- PD history (time since diagnosis of PD, duration of levodopa treatment, time since onset of wearing off episodes)

- Total daily levodopa dose, number of levodopa doses per day

- PD disease severity (Modified Hoehn and Yahr Staging in "ON" State)

- UPDRS Part 3 Motor score in ON/OFF (from screening assessment); the change from OFF to ON state in UPDRS part 3 Motor score at the Screening will also be classified as ≥6 points, or ≥11 points reduction.

- Baseline Dyskinesia (Dyskinetic before TV1, Non-dyskinetic before TV1). The classification will be done based on the Parkinson's disease diary data. The patients who have recorded at least 1 hour of dyskinesia (either ON with non-troublesome dyskinesia or ON with troublesome dyskinesia) on at least 2 days before TV will be classified as dyskinetic.

- Proportion of patients with FEV1 <60% of predicted or FEV1/FVC ratio <70% at baseline versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70% (based on the randomization strata).

- Screening spirometry data: FEV1, FVC, and FEV1/FVC ratio, presented for each motor status, ON or OFF, separately.

Demographics and PD disease data will also be summarized by subgroups (Patients with baseline PD severity < 2.5 points on the Hoehn & Yahr scale versus ≥ 2.5 points; Patients who are dyskinetic before TV1 versus non-dyskinetic; Patient with the baseline daily levodopa dose less than or equal to the median versus above median; Patients who have less than 4.5 hours of PD diary mean daily OFF time before TV1 versus 4.5 hours or more; Patients with FEV1 <60% of predicted or FEV1/FVC ratio <70% at baseline versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%, Non-elderly (<65 years) versus elderly (≥65 years) patients, Female versus Male patients).

7.3. MEDICAL HISTORY

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. The medical history data will be summarized with frequencies and percentages of patients with at least one medical history item, and patient frequencies and percentages on the system organ class (SOC) and preferred term (PT) levels. The events will also be summarized. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. The medical history will be summarized based on the baseline definition, see Section 6.2.

7.4. MEDICATION

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), Q1March2014.

For the medications recorded on CRF page "Prior and Concomitant Medications", medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of inhaled CVT-301 dosing will be considered concomitant medications.

Summaries of baseline PD treatment medications (medications which start with ATC code N04) will be presented in tabular form using the ATC Level 4 and preferred term. Other prior medications and concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and PT. Frequencies and percentages will be presented by treatment group and overall. The counts of medications will also be summarized. The tables will be sorted by overall descending frequency of ATC Level(s) and then, within an ATC Level, by overall descending frequency of PT.

If the medication start date is incomplete, then it will be imputed as follows for the

purpose of determining concomitance only:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitance only:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

8. EFFICACY

The efficacy evaluation defined below includes data from the patients who were previously enrolled in the CVT-301-004 study and for the CVT 301 naïve patients (including patients from CVT-301-005 observational arm). The data from patients who were enrolled to study CVT-301-003 or CVT-301-009 will not be included in the efficacy summaries and will be listed only.

In general, for the purpose of the efficacy analyses, the visits will be pooled as follows:

	Study CVT-301-004				Study CVT-301-004E			
Treatment/study group	**Baseline visit**	**Week 4 visit**	**Week 8 visit**	**Week 12 visit**	**Baseline visit**	**Month 1 visit**	**Month 3-9 visits**	**Month 12 visit**
CVT-301-004, CVT-301 group	Baseline	Month 1	not used	Month 3	not used	not used	Months 6-12	not used
CVT-301-004, placebo group	not used	not used	not used	not used	Baseline	Month 1	Months 3-9	Month 12
CVT-301 naïve patients	NA	NA	NA	NA	Baseline	Month 1	Months 3-9	Month 12
CVT-301-005, Observational, Arm	NA	NA	NA	NA	Baseline	Month 1	Months 3-9	Month 12

8.1. EFFICACY ENDPOINTS AND ANALYSES

The ITT population will be used for the efficacy analysis. Patients will be analyzed according to randomized treatment group. The changes within each treatment group and the overall change from baseline in continuous efficacy variables will be estimated using an MMRM. Although the focus of this study is to describe the within-group changes, the differences between the treatment groups will be estimated as well, but no inferential analyses regarding the between-group differences will be done. The model will include visit, stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC), treatment group, treatment/study group, and the interaction between the treatment group and visit as fixed factors as fixed factors. The baseline value will be used as a covariate. An unstructured covariance structure will be applied for the MMRM. In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) or the heterogeneous Toeplitz structure (TOEPH). 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.

For all patients, categorical data will be evaluated descriptively. Each visit will be evaluated separately for the categorical endpoints. The efficacy endpoints and associated analyses are as follows. For the detailed definition of the endpoints, see Section 4.3.

- Resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic and maintaining the ON at 60 minutes after study drug administration (per the examiner's subjective assessment). This endpoint will be based on the examiner's subjective assessment. The proportions of patients will be summarized descriptively for each CVT-301 treated patients. The missing values will be counted as non-resolved. The data will be summarized with descriptive statistics within each treatment group and overall. The GLIMMIX procedure for binomial data with logic link will be used to estimate the treatment group difference. Factors similar to the ones used described above will be included in the model (sensitivity method). An unstructured covariance structure will be used. The missing data will not be imputed as non-responders in this sensitivity analysis. Below sample code will be used for analysis.

```
proc glimmix data=t2212;
class pdsevbl fev1bl trtpn avisitn stdygrp usubjid;
model avalc(event='Y')= updoffsc pdsevbl fev1bl stdygrp trtpn avisitn trtpn*avisitn/s  dist=binary link=logit cl
oddsratio (diff=first) solution;
random avisitn/subject=usubjid residual type=un ;
lsmeans  avisitn*trtpn/ cl ilink;
ods output tests3=PVAL lsmeans=lsmeans(keep=trtpn avisitn mu) estimates=estimates(keep=statement label
expestimate explower expupper);
/* tv4 */
estimate "tv4 trt 2 vs 1" trtpn -1 1   trtpn*avisitn  0 0 0 -1 0   0 0 0 1 0  /cl or e;
run;
```

- Change from baseline (3 consecutive days prior to TV1) in patient-recorded total daily OFF time, assessed by the patient and recorded in the PD Diary for 3 consecutive days prior to the visit. Similar methods as for primary endpoint will be used. The baseline daily OFF time will be used as a covariate in the MMRM. Only valid diary days will be included in the diary summarizations. In addition, change from baseline in total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia and total daily ON time with troublesome dyskinesia will be analyzed similarly using the MMRM. For the total daily OFF time only, MI analysis will be performed as a sensitivity analysis and subgroup analysis on subgroups in section 6.6 will also be prepared.

- The PGI-C score. The proportions of patients who improved (much improved, improved or a little improved) will be tabulated by visit for CVT-301 treated

patients. This summary will be complemented by the distribution of each response category (much improved, improved, a little improved, no change, a little worse, worse, much worse) tabulated by the treatment group. The data will be summarized with descriptive statistics within each treatment group and overall.

- Changes from baseline in endpoints based on S&E ADL score, UPDRS Part 2 score, PHQ-9 total score, and PDQ-39 sub-scores and index score. An ANCOVA model with the treatment group, treatment/study group and stratification variables as fixed factors and the baseline value as a covariate will be used to estimate the treatment group differences. In addition, the data will be presented with descriptive statistics classified by treatment group and visit. The observed cases will be used in the analysis and summaries.

- Change from baseline (TV1) and Last Day of Treatment (LDOT) to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after TV6 in the PHQ-9 will be summarized descriptively. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.

Sensitivity analyses of the efficacy data

The following sensitivity analysis will be performed for the daily OFF time efficacy endpoint.

- MI analysis: MI techniques based on Pattern Mixture Models (PMM) will be applied (Ratitch et al., 2011) as a further sensitivity analysis in the ITT population. This methodology will structure data based on missing data patterns. The method will be based on a missingness pattern having a monotone structure, i.e. if among the observations over time one data value is missing, all other values after this missing value will also be treated as missing. For patients with intermittent missing values, before performing MI based on the PMM, it will be necessary to create a monotone missingness pattern. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. The MI procedure in SAS will be used for this purpose and this first MI step is planned to be repeated 100 times, creating several different datasets with a monotone missing data structure. Seed value of 201508 will be used in the MI procedure. The imputation is based on the missing at random (MAR) assumption, i.e. the missing data are assumed to follow the same model as the other patients in their respective treatment group that have complete data.

  After this, the remaining missing data can be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the created datasets with a monotone missing data pattern, the MI procedure in SAS will used to

impute missing values based on a sequential procedure reflecting the monotone missing data pattern. Patients with the first missing value occurring at visit at Month 1 will have their missing Month 1 value replaced by an imputed value from a regression model with baseline value, treatment group, treatment/study group and the stratification factors as explanatory variables. In the next step, patients with their Month 3 value missing will have their missing Month 3 value replaced by an imputed value from a regression mode with baseline value, treatment group, treatment/study group and stratification factors and the Month 1 value as explanatory variables. Similar procedure will be used to replace the missing values at Month 6, 9 and 12.

The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the exploratory efficacy endpoint. MMRM models similar as described above will thus be run on each of the generated imputed datasets. Finally, the MIANALYZE procedure in SAS will be applied to combine the results from these several datasets to derive an overall estimate of the within-group changes.

Exploratory analyses of the efficacy data

- Changes from baseline in endpoints based on S&E ADL score, UPDRS Part 2 score, PHQ-9 total score, Impact of Parkinson's OFF Episodes Patient Survey score along with numeric individual score (i.e. Impact of OFF Time on Disability - ON State Disability and Impact of OFF Time on Disability - ON State Disability), and PDQ-39 sub-scores and index score. An ANCOVA model with the treatment group, treatment/study group and stratification variables as fixed factors and the baseline value as a covariate will be used to estimate the treatment group differences. In addition, the data will be presented with descriptive statistics classified by treatment group and visit. The observed cases will be used in the analysis and summaries.

- For Impact of Parkinson's OFF Episodes Patient Survey, the frequency and percentage of patients for each response will be summarized by treatment group and overall for each of the item within each section.

9. SAFETY

The population used for safety analyses will be the Safety Population. The analyses are outlined below. The safety evaluation defined below includes data from all patients included in the Safety population.

For the statistical analysis of the spirometry data, the visits will be pooled as described in Section 8. Otherwise, all safety data will be presented in the summaries,

9.1. SPIROMETRY

For CVT-301-naïve patients and CVT-301-009 patients, spirometry will be assessed at the neurology sites for screening and TV1 and the pulmonary sites will be exclusively responsible for the conduct of spirometry after TV1 (within 2 weeks prior to the 3-, 6-, 9-, and 12-month visits, and 4 to 5 weeks following completion of Treatment Visit 6 [TV6]). For patients from CVT-301-004, spirometry will be assessed at the neurology sites at TV1, and the pulmonary sites will be exclusively responsible for the conduct of spirometry after TV1 as described for the CVT-301-naïve patients. Spirometry data obtained in the study site will reviewed by a central spirometry laboratory (Biomedical Systems, Inc.) which will provide a quality over read of all evaluations based on acceptability and repeatability metrics in accordance with ATS criteria. FEV1, FVC and FEV1/FVC ratio will be recorded from the single "best test" (based on effort with highest summed FEV1 and FVC). Variables will include the absolute FEV1, FVC, and FEV1/FVC ratio and FEV1 and FVC expressed as % of predicted value.

The variables from pulmonary laboratory will include the FEV1, FVC, FEV1/FVC ratio, DLCO, IVC, SVC and VA. FEV1 and FVC expressed as % of predicted value, predicted DLCO, hemoglobin (Hb) adjusted predicted DLCO, and DLCO expressed as % of these predicted values will be calculated per the method in section 6.2. The following analysis will be performed:

All the parameters collected at the pulmonary laboratory as well as the % of predicted DLCO and % of Hb adjusted predicted DLCO will be summarized descriptively by treatment group and overall. In addition, the data will be summarized by treatment/study group.

- Change from baseline to other visits for each parameter.
- Number and percentage of patients with FEV1/FVC < 60% and <70% by visit
- DLCO data will also be provided to indicate whether specific determinations met American Thoracic Society (ATS) quality criteria. The proportion of DLCO/spirometry data measurements meeting or not meeting ATS quality criteria will be summarized by treatment group and overall.

- Categories of changes (<-50%, -50% -<-40%, -40% -<-30%, , -30% -<-20%, , -20% -<-10%, -10% -<-10%, 10% -<20% , 20% -<30% , 30% -<40% , 40% -<50%, >=50%) from baseline for FEV1, FEV, FEV1/FVC ratio and DLCO by visit. The summary for FEV1 will also be provided by smoker status.

The descriptive summaries will be repeated for the subset of assessments meeting the ATS quality criteria.

Another subset analysis will be performed by excluding the DLCO data from patients with a very high intra-individual variability. For the purpose of this analysis, all patients who have a co-efficient of variation (CV) value >7.5% for FEV1 will be excluded. The CV will be calculated for each patient as standard deviation divided by the mean.

In addition to the descriptive statistics, the changes in the FEV1, FEV1/FVC ratio, and DLCO values within each treatment group and differences between the treatment groups will be estimated with MMRM. The model will include the treatment group (CVT-301 DL1 or CVT-301 DL2), treatment/study group (patients who received inhaled CVT-301 in CVT-301-004 study, patients who received placebo in CVT-301-004 study and CVT 301 naïve patients), visit (visits at 1, 3, 6, 9, and 12 months), 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 baseline spirometry value 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 least square (LS) mean, standard error, and LS mean difference for the changes from baseline within each treatment group and overall, and between the treatment group at each visit; along with the 95% confidence interval (CI) will be provided in a table. Treatment group difference will be assessed with a 2-sided alpha level of 0.05, unless specified otherwise.

The SAS code planned for the analysis is outlined below.

```
proc mixed data=&data;
class pdsevbl fev1bl trta stdygrp avisit usubjid;
model chg=base pdsevbl fev1bl stdygrp avisit trta trta*avisit / ddfm=kr;
repeated avisit / subject=usubjid(trta) type=un;
lsmeans trta*avisit / cl pdiff;
ods output Diffs=DIFF_MI LSMeans=LSM_MI tests3=tests ;
run;
```

Statistical Analysis Plan

The safety population will be used for the descriptive analysis. The CVT-301-003 and CVT-301-009 rollover subjects will be excluded for MMRM analysis.
In addition, the changes in the spirometry values within treatment arm in CT-301-004 (CVT-301 vs Placebo) and differences between the CVT-301-004 treatments (CVT-301 vs Placebo) will be estimated with MMRM. The model will include the treatment group (CVT-301 DL1 or CVT-301 DL2), CVT-301-004 treatment, visit (visits at 1, 3, 6, 9, and 12 months), the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) and the interaction between CVT-301-004 treatment and visit as fixed factors. The baseline spirometry value 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 least square (LS) mean, standard error, and LS mean difference for the changes from baseline within CVT-301-004 treatment, and between the CVT-301-004 treatment arm at each visit; along with the 95% confidence interval (CI) will be provided in a table. CVT-301-004 treatment arm difference will be assessed with a 2-sided alpha level of 0.05, unless specified otherwise.

The SAS code planned for the analysis is outlined below.

```
proc mixed data=&data;
class pdsevbl fev1bl trta stdygrp avisit usubjid;
model chg=base pdsevbl fev1bl stdygrp avisit trta stdygrp*avisit /
ddfm=kr;
repeated avisit / subject=usubjid(stdygrp) type=un;
lsmeans stdygrp*avisit / cl pdiff;
ods output Diffs=DIFF_MI LSMeans=LSM_MI tests3=tests ;
run;
```

The CVT-301-004 rollover patients in safety population will be used for the analysis.

Sensitivity analyses of the spirometry data

The following sensitivity analysis will be performed for FEV1, FEV1/FVC and DLCO assessments.

- MI analysis: MI techniques based on Pattern Mixture Models (PMM) will be applied (Ratitch et al., 2011) as a further sensitivity analysis in the Safety population. This methodology will structure data based on missing data patterns. The method will be based on a missingness pattern having a monotone structure, i.e. if among the observations over time one data value is missing, all other values after this missing

value will also be treated as missing. For patients with intermittent missing values, before performing MI based on the PMM, it will be necessary to create a monotone missingness pattern. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. The MI procedure in SAS will be used for this purpose and this first MI step is planned to be repeated 100 times, creating several different datasets with a monotone missing data structure. Seed value of 201508 will be used in the MI procedure. The imputation is based on the missing at random (MAR) assumption, i.e. the missing data are assumed to follow the same model as the other patients in their respective treatment group that have complete data.

After this, the remaining missing data can be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the created datasets with a monotone missing data pattern, the MI procedure in SAS will used to impute missing values based on a sequential procedure reflecting the monotone missing data pattern. Patients with the first missing value occurring at visit at Month 1 will have their missing Month 1 value replaced by an imputed value from a regression model with treatment group, treatment/study group, baseline spirometry value, the stratification factors and the interaction between the treatment group and visit as explanatory variables. In the next step, patients with their Month 3 value missing will have their missing Month 3 value replaced by an imputed value from a regression model with treatment group, treatment/study group, baseline spirometry value, stratification factors, the interaction between the treatment group and visit and the Month 1 value as explanatory variables. Similar procedure will be used to replace the missing values at Month 6, 9 and 12.

The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the primary endpoint. MMRM models similar as described above will thus be run on each of the generated imputed datasets and the difference between the treatment groups will be estimated. The MMRM model will be similar to the primary analysis. Finally, the MIANALYZE procedure in SAS will be applied to combine the results from these several datasets to derive an overall estimate of the within-group changes and treatment group differences. Estimates and corresponding 95% confidence intervals will be calculated.

The following summary will be performed on the neurology sites data.

- Change from baseline to other visits for each parameter. The baseline is defined as the last arrival assessment before the first dose of inhaled CVT-301. If the Arrival value is missing, the last available value in ON state before the first dose

of study drug will be used. The summary for FEV1 will also be provided by smoker status.

- Number and percentage of patients with FEV1/FVC < 60% and <70% by visit
- Spirometry data will also be provided to indicate whether specific determinations met American Thoracic Society (ATS) quality criteria. The proportion of DLCO/spirometry data measurements meeting or not meeting ATS quality criteria will be summarized by treatment group and overall. The summary will also be performed for ON state measurements, OFF state measurements, and all measurements, separately. The reasons for not meeting ATS quality criteria will be summarized, as data allow.
- Categories of changes (<-50%, -50% -<-40%, -40% -<-30%, , -30% -<-20%, , -20% -<-10%, -10% -<-10%, 10% -<20% , 20% -<30% , 30% -<40% , 40% -<50%, >=50%) from baseline for FEV1, FEV, FEV1/FVC ratio and DLCO by visit. The summary for FEV1 will also be provided by smoker status.
- Actual values and change from pre-dose to post-dose time points for each parameter at TV1; percent change for FEV1 and FVC will also be summarized. If a pre-dose value at TV1 is missing, the last available value in OFF state before the first dose of will be used. The summary for FEV1 will also be provided by smoker status.
- Number and percentage of patients with percent of changes (<-50%, -50% -<-40%, -40% -<-30%, -30% -<-20%, -20% -<-10%, -10% -<10%,10% -<20% , 20% -<30% , 30% -<40% , 40% -<50%, >=50%) at each post-dose time point at TV1 from pre-dose for FEV1, FVC and FEV1/FVC. The summary for FEV1 will also be provided by smoker status.

9.2. EXTENT OF EXPOSURE

The following information will be summarized by treatment group and overall:

- The number of patients with dose change
- Duration of exposure to CVT-301 inhalations (days)
- Total exposure to CVT-301 inhalation, expressed as person years (sum of exposure to CVT-301 inhalations over all patients, classified by treatment group)
- Total number of doses and capsules taken, by visit and overall. Average number of daily doses and number of capsules, by visit and overall
- Proportion of days with 5, 4, 3, 2, 1 or 0 doses administered
- Proportion of patients using 5, 4, 3, 2, 1 or 0 doses/day at least once

In addition, these in-clinic data will be summarized by treatment group and visit:

- Standard morning dose of LD-containing medications to in-clinic OFF (mins)
- In-clinic OFF to start of study drug inhalation (mins)
- Standard morning dose of LD-containing medications to start of study drug inhalation (mins)
- Duration of study drug inhalation (mins), calculated as (Completion time of last inhalation - Time of start of first capsule inhalation).

Furthermore, the distribution of time of intake of study medication (00:00 - 00:30, 00:30 - 01:00, ...) as percentage of the total number of study medication intakes will be displayed during the whole treatment period. This data will be collected on the Inhaled Dosing Log.

In addition, all the data will be broken down by treatment/study group. All study drug data will be listed. A listing will also be provided to show how many times each patient will take study drug and the capsules taken for each day.

9.3. TREATMENT COMPLIANCE

Patients will be instructed to administer inhaled study drug up to 5 times each day during the treatment period. In-clinic administration of study drug will be supervised by study personnel, and at-home diary data will be reviewed to ensure patient compliance. Since there are no fixed scheduled doses for each day, compliance will not be calculated for this study; alternatively, study drug use will be evaluated based on the inhaled medication treatment log by summarizing the proportion of days with >5, 5, 4, 3, 2, 1 or 0 doses administered.

9.4. ADVERSE EVENTS

All AEs will be coded using the MedDRA version 17.0.

Treatment-emergent adverse events (TEAEs) are defined as all AEs that start after the patient receives the first dose of CVT-301 after the relevant baseline (see Section 6.2 for the definition of baseline). Events will be classified as drug-related if the AE is classified as possibly, probably, or definitely related to study drug.

Events with a missing start time, but with a start date equal to the date of first dose of study drug will be considered treatment-emergent. If the AE start date is incomplete, then it will be imputed as follows for the purpose of determining TEAE:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.

- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

The original date and time will be shown on all listings of AEs. Listings will be provided for all AEs, serious AEs, AEs leading to study drug discontinuation, AEs leading to dose reduction, and deaths.

TEAEs will be summarized by SOC and PT for each treatment group and CVT-301 overall. TEAEs with onset after the treatment period are attributed to the treatment group during the treatment period. Both event and patient counts, where applicable, will be summarized. The counts will be complemented by percentages will be calculated for the patient counts unless otherwise specified. In addition, the incidence of TEAEs, normalized for duration of exposure to CVT-301 will be presented (number of TEAEs divided by the total exposure to CVT-301, measured as patient years).

- An overall summary of the number and percentage of patients reporting TEAEs and the number of TEAE events, drug-related TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to dose interruption, TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction and TEAEs leading to death
- TEAEs by SOC and PT, both as event and patient counts
- TEAEs by PT, both as event and patient counts
- Drug-related TEAEs by SOC and PT, both as event and patient counts
- Severe TEAEs by SOC and PT, both as event and patient counts
- Drug-related TEAEs by SOC, PT and severity, as event counts; percentages will be calculated for the event count out of total number of events
- Drug-related TEAEs by SOC, PT and relationship, as event counts; percentages will be calculated for the event count out of total number of events
- Serious TEAEs by SOC and PT, both as event and patient counts
- TEAEs leading to study drug interruption, both as event and patient counts
- TEAEs leading to study drug withdrawal, both as event and patient counts
- TEAEs leading to dose reduction, both as event and patient counts
- Most common AEs, both as event and patient counts, most common TEAEs is defined any AE preferred term occurred in greater than 10% total patients
- Time to first onset of most common AEs, classified as 0-1 months, >1-3 months, >3-6 months, >6-9 months and after 9 months, where the date of TEAE onset will be used as the time point for classification

The tables will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT based on the patient count for the total column. If only event count is presented, the sorting will be done based on the event count.

In addition, selected AE tables will be broken down by treatment/study group.

9.5. LABORATORY EVALUATIONS

Laboratory samples for hematology and clinical chemistry will be analyzed by a central laboratory (located in the United States of America) 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.

All parameters will be converted to consistent units according to the International System of Units (SI) before summarization. The following will be summarized by treatment group and overall:

- Actual values and change from baseline, if applicable, at each visit for each parameter (for handing of data from the ET visit, see Section 6.4)
- Number and percentage of patients with normal or "abnormal" (i.e., out of reference range) labs at each visit for each parameter
- Number and percentage of patients with potentially clinically significant (PCS) lab values at each visit for each parameter
- Number and percentage of patients with potentially clinically significant changes (PCSC) in lab values at each post-baseline visit for each parameter

PCS and PCSC will be identified for specific laboratory parameters as outlined in the following table.

Laboratory Parameter	Units	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Changes from baseline values)	
		High	Low	% increase	% decrease
Hemoglobin	g/L	> 10 above ULN	>20 below LLN	NA	25%
Hematocrit	L/L	>0.04 above ULN	>0.05 below LLN	NA	25%
WBC	GI/L	>5 above ULN	>1 below LLN	100%	50%
Neutrophils	GI/L	NA	<0.5xLLN	100%	50%
Neutrophils	%	NA	<0.5xLLN	100%	50%
Lymphocytes	GI/L	NA	<0.5xLLN	100%	50%
Lymphocytes	%	NA	<0.5xLLN	100%	50%

Total bilirubin	µmol/L	>1.5xULN	NA	300%	NA
Total protein	g/L	>15 above ULN	>15 below LLN	200%	60%
Albumin	g/L	>5 above ULN	>5 below LLN	NA	60%
AST	U/L	>3xULN	NA	300%	NA
ALT	U/L	>3xULN	NA	300%	NA
Alkaline Phosphatase	U/L	>3xULN	NA	300%	NA
GGT	U/L	>3xULN	NA	300%	NA
Creatinine	µmol/L	>1.5xULN	NA	200%	NA
Urea	mmol/L	>2.5xULN	NA	300%	NA
Uric Acid	µmol/L	>3xULN	NA	300%	NA
Sodium	mmol/L	>5 above ULN	>5 below LLN	10%	10%
Potassium	mmol/L	>1 above ULN	>0.5 below LLN	25%	20%
Carbon dioxide	mmol/L	>40	<16	25%	25%
Calcium	mmol/L	>2.99	<1.78	30%	30%
Glucose (fasting)*	mmol/L	>11.1	<2.8	300%	40%

ULN = Upper limit of normal range, LLN = Lower limit of normal range
Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients. ' * fasting defined as ≥4 hr from prior meal
The tables showing the normal/abnormal values, PCS values and PCSCs will be done both as summaries of all data and as shift tables (i.e., classified by the baseline status).

Values which fall outside the central laboratory normal range will be flagged as "L" - below normal range, or "H" - above normal range, on the data listings. PCS and PCSC values will also be flagged. All repeated values will be presented on the data listings but not included in the summaries showing data by visit.

9.6. VITAL SIGNS

Standard vital sign measurements will include RR, systolic and diastolic BP (SBP, DBP), and HR. 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. Orthostatic vital sign measurements will include SBP, DBP, and HR.

The following will be summarized:

- Change from baseline to other visit pre-dose values for each parameter. Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients. '

- Actual values and change from pre-dose to post-dose time points at TV1 by time point for each parameter
- Number and percentage of patients with PCS values at each applicable visit and time point for each standard vital sign parameter
- Number and percentage of patients with PCSC values at each applicable visit and time point for each standard vital sign parameter
- Number and percentage of patients with Orthostatic hypotension at each applicable visit

PCS and PCSC for standard vital sign will be identified as outlined in the following table.

Vital Sign	Units	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Change from Baseline or pre-dose values *)	
		High	Low	increase	decrease
Pulse rate	bpm	>120	<40	100	50
Respiration Rate	brpm	>32	<8	50	NA
Systolic Blood Pressure (supine)	mmHg	>200	<85	60	20
Diastolic Blood pressure (supine)	mmHg	>120	<40		0.2x
*Pre-dose values will be used for corresponding post-dose values assessment at TV1. Otherwise baseline values are used.					

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 supine/semi-supine measurement.

9.7. 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).

The following will be summarized:

- Change from baseline to other visit pre-dose values for each parameter. Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients. '.

- Number and percentage of patients with PCS values at each applicable visit for each parameter
- Number and percentage of patients with PCSC values at each applicable visit for each parameter

PCS and PCSC will be identified as outlined in the following table.

ECG	Units	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	increase	decrease
PR interval	msec	>300	NA	>25% for baseline ≥200 >50% for baseline <200	NA
QRS interval	msec	>200	NA	>25% for baseline ≥100 >50% for baseline <100	NA
QTcB	msec	>500	NA	>15% for baseline ≥440 >30% for baseline <440 >30 msec increase >60 msec increase Change>30 and value>500 Change>60 and value>500	NA
QTcF	msec	>500	NA	>15% for baseline ≥440 >30% for baseline <440 >30 msec increase >60 msec increase Change>30 and value>500 Change>60 and value>500	NA
Heart Rate	bpm	>120	<35	NA	NA

9.8. 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 following will be summarized:

- Total number and percentage of patients reporting abnormal clinically significant physical examination results

9.9. 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. All C-SSRS data will be listed. The frequency and percentage of patients with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized as appropriate by treatment group and overall.

A shift table from baseline to each visit, days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after LDOT will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.

A shift table from LDOT to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after TV6 will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.

9.10. EPWORTH SLEEPINESS SCALE

The Epworth Sleepiness Scale is used to determine the level of daytime sleepiness. There are 8 situations listed 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). The total score is the sum of 8 item scores and can range between 0 and 24. In case of missing item scores, the missing value will be replaced by the average of non-missing scores at the same visit from the same patient. In case all item scores are missing, the total score will be set as missing. The higher total score indicates the higher level of daytime sleepiness. A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy.

All Epworth Sleepiness Scale data will be listed. The total score and change from baseline to each visit will be summarized by treatment group and overall (for handing of data from the ET visit, see Section 6.4). The total score and change from baseline (TV1) and Last Day of Treatment to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment will also be summarized. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.

9.11. 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 any impulsive control disorder (gambling, sexual, buying, and eating disorders); Section 2 assesses other compulsive behaviors (punding, hobbyism, and walkabout); and Section 3 assesses compulsive medication use.

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The frequency and percentage of patients with positive response for each of the item within each section will be summarized by treatment group and overall. The assessment of positive response for each item will be based on the table below.

Section and Item	Number of items with positive response
A. Impulse Control Disorders	
Compulsive gambling	any 2 of the 5 gambling items
Compulsive sexual behavior	any 1 of the 5 sexual behavior items
Compulsive buying	any 1 of the 5 buying items
Compulsive eating	any 2 of the 5 eating items
B. Other Compulsive Behaviors	
Hobbyism	item #1A
Punding	item #1B
Walkabout	item #1C
C. Compulsive Medication Use	items #1 and #4

9.12. UPDRS PART 4

Changes from TV1 (pre-dose) to each visit (pre-dose) in UPDRS Part 4 sum scores and each sub-scores (Dyskinesias and Fluctuations)will be summarized and analyzed using similar MMRM methods as for the spirometry data.

9.13. EXAMINER-RATED DYSKINESIA

The occurrence and severity will be tabulated by treatment group and visit. The observed cases will be used in the summaries. No formal statistical methods will be used.

9.14. AMPHETAMINE WITHDRAWAL QUESTIONNAIRE (AWQ)

The actual values and changes from baseline (TV1) and LDOT to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after LDOT in AWQ total score will be summarized descriptively for patients in safety population. LDOT is defined as assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.

9.15. DOPAMINE DYSREGULATION SYNDROME - PATIENT AND CAREGIVER INVENTORY (DDS-PC)

The actual values and changes from baseline (TV1) and Last Day of Treatment to days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment in DDS-PC total score will be summarized descriptively for patients in safety population. LDOT is defined as

assessment taken on TV6 or ET for patients who didn't enrolled into the sub-study and TV4, TV5 or TV6 for patients who enrolled into sub-study.

9.16. MOVEMENT DISORDER SOCIETY - UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

The MDS-UPDRS Part 1 and Part 2 value will be summarized descriptively on days 1, 3, 6, 8, 11, 14, 17, 24, and 28 after Last Day of Treatment by treatment for patients in the safety population.

9.17. UPDRS PART 1

The actual values and changes from baseline to each visit (pre-dose) in UPDRS Part 1 total score will be summarized using observed data. The total score will be calculated as the sum of the individual items 1 to 4. Missing individual items will not be imputed and the sum score will be missing in case of 1 or more missing items.

10. INTERIM ANALYSES

Two interim analyses are planned. The first interim analyses were based on interim analysis SAP version 1.0 and data cut on Feb 10th, 2017. The second interim will be based on this SAP and planned data cut June 30, 2017.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The protocol stated that the data for patients who were enrolled in the CVT-301-004 study, the CVT-301-009 study and for the CVT-301-naïve patients study will be primarily analyzed together, while the patients who were enrolled in the CVT-301-003 study will be analyzed separately. In the SAP, the patients enrolled from CVT-301-003 and CVT-301-009 will not be included in efficacy summaries (i.e. the patients enrolled from CVT-301-003 and CVT-301-009 will be excluded from ITT population) due to the different study designs. Instead the efficacy data from patients who were enrolled in the CVT-301-003 or CVT-301-009 study will be analyzed separately, as data listings. The rationale for excluding the CVT-301-003 patients from the efficacy summaries is the gap between the end of CVT-301-003 and start of CVT-301-004E.

12. PROGRAMMING CONSIDERATIONS

All tables, listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA) or higher. Computer-generated table, listing and figure output produced by INC Research will adhere to the following specifications.

12.1 GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

12.2 TABLE, LISTING, AND FIGURE FORMAT

12.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified. For spirometry graphs, separate colors will be used for ON (red circles) and OFF (blue triangles) State data.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used.
- Mixed case will be used for all titles, column headers, and programmer-supplied formats, as appropriate.

12.2.2 Headers

- All output should have the following header at the top left of each page:
  Civitas Therapeutics, Inc.
  Protocol No. CVT-301-004E Confidential
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date and time (date and time output was generated) should appear along with program name and location as the last footer on each page.

12.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). The title is centered. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

12.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatment group in the tables will be DL1 first, followed by DL2 and an overall column (if applicable in tables).

12.2.5 Body of the Data Display

12.2.5.1 General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

12.2.5.2 Table Conventions

- Units will be included where available

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Min, Max	XXX,XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999 then present as >0.999.
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count, e.g., 7 (12.8%), 13 (5.4%). For a value that rounds down to 0.0, display it as "<0.1". Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator, unless specified otherwise. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

12.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of patient number, visit/collection day, and visit/collection time.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000).
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26).

12.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date and time the program was run.

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13. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS programs.

INC Research SOP 03.009.00 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

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Abuse Assessment Methodology and Adverse Event Terms

A pre-NDA meeting was held with the Agency on 28 September 2016 (see FDA pre-NDA Meeting Minutes) to gain agreement on the adequacy of the nonclinical and clinical program and content and format and assessment of abuse potential for the 505(b)(2) NDA for CVT-301. In the CVT-301 Pre-NDA Meeting Package submitted to IND 115750 in Sequence 086 on 25 August 2016, Acorda provided a Draft Abuse Potential Assessment report and indicated that abuse related adverse event terms were assessed based on the terms published by Love and Sun (2013) for the completed clinical studies and for the clinical study reports and Integrated Summary of Safety for the ongoing clinical studies. In the CVT-301 pre-NDA Meeting minutes regarding question 4a, "*Does the Division agree with the plan for assessment and reporting of abuse potential?*" The Division indicated in the FDA Response to Question 4a, point 5, that the following AE terms were of particular interest:

> *"5. Because abuse of levodopa is mainly known in the population of patients with PD, your Abuse Potential Assessment Report, in which you plan to include the analysis of published literature, should include the following items:*
> - *Populations: analysis should to be performed separately for PD patients and healthy subjects*
> - *For the PD study population, the following adverse events are of particular interest: abuse, misuse, withdrawal, dependence, dopamine dysregulation syndrome, hedonistic homeostatic dysregulation, euphoria, high, overdose, misuse, diversion, hoarding of medication, neuroleptic malignant syndrome, hyperpyrexia and confusion, rebound*
>
> *6. Search and analysis of adverse events from your clinical data and the post-marketing data for levodopa formulations in publically available data bases should include and use the same search terms listed above in point 5."*

In 2016 the International Society for Central Nervous System Clinical Trials and Methodology (ISCTM) recommended a list of 41 adverse event terms for assessment of abuse potential (Setnik 2016). Subsequent to the Pre-NDA meeting the FDA also issued a new Final Guidance, FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (January 2017) that included 19 adverse event terms for assessment of abuse potential. Therefore, based on the FDA recommendations and more recent publications, Acorda has modified its methodology for assessment of abuse potential based on the list of 213 adverse event terms published by Love and Sun (2013). Instead, Acorda is using a shorter more focused composite list of 73 adverse event terms including the 15 terms recommended by FDA in the CVT-301 FDA pre-NDA Meeting Minutes (October 2016), the 19 terms from the new FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (January 2017) and the 41 terms recommended by ISCTM (Setnik 2016). Note, two terms (euphoria and drug withdrawal) are repeated in two of the lists. All of these terms except hedonistic hemostatic dysregulation have been converted into MedDRA, Version 19.0 Preferred Terms (PT). Because there was no MedDRA conversion term for the verbatim term hedonistic hemostatic dysregulation it was included in the composite list of 73 MedDRA terms. The MedDRA PT may provide abuse-related information about a drug, and

were used for assessment of abuse related adverse events in the CVT-301 clinical studies and Integrated Summary of Safety. The verbatim adverse event terms and MedDRA PT are provided in Table 1.

Table 1: Drug Adverse Event Terms for Abuse Potential Assessment of CVT-301 Safety Data

15 Adverse Event Terms From CVT-301 Pre-NDA Meeting Minutes, page 5, FDA Response to Question 4b, Item 5 (October 2016)
Abuse, misuse, withdrawal, dependence, dopamine dysregulation syndrome, hedonistic homeostatic dysregulation, euphoria, high, overdose, diversion, hoarding of medication, neuroleptic malignant syndrome, hyperpyrexia, confusion, rebound
19 Adverse Event Terms From FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (January 2017)
Euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect, somnolence, mood disorders and disturbances, psychosis, aggression, confusion, disorientation, drug tolerance, habituation, drug withdrawal syndrome, substance related disorders
41 Adverse Event Terms From Setnik, B. A Consensus List Proposal For Adverse Events Related To Abuse And Dependence Potential (Setnik 2016)
Abnormal behavior, abnormal thinking, agitation, cognition disorder, concentration impaired, concentration loss, confusion and disorientation, confusional state, delirium, delusional disorder unspecified type, detachment, disturbance in attention, elation inappropriate, elevated mood, emotional disorder, euphoria/euphoric mood, exhilaration inappropriate, feeling abnormal, feeling drunk, feeling happy inappropriately, flight of ideas, hallucination(visual and auditory), inappropriate affect, inappropriate, elation, inappropriate, laughter, inappropriate mood, elevation, irritability, memory impairment, mental disorder

MedDRA Preferred Terms based on the composite list of 73 Adverse Event Terms
Abnormal behavior, acute psychosis, aggression, agitation, cognitive disorder, confusional state, delirium, delirium tremens, delusional disorder unspecified type, delusional perception, dependence, disorientation, dissociation, disturbance in attention, dizziness, dopamine dysregulation syndrome, drug abuse, drug abuser, drug dependence, drug diversion, drug tolerance, drug withdrawal convulsions, drug withdrawal syndrome, elevated mood, emotional disorder, euphoric mood, feeling abnormal, feeling drunk, feeling of relaxation, flight of ideas, hallucination, hallucination auditory, hallucination gustatory, hallucination mixed, hallucination olfactory, hallucination synanesthetic, hallucination tactile, hallucination visual, hedonistic homeostatic dysregulation[a], hyperpyrexia, inappropriate affect, intentional overdose, intentional product misuse, irritability, medication overuse headache, memory impairment, mental disorder, mental impairment, mood altered, mood swings, neuroleptic malignant syndrome, overdose, paranoia, parkinsonism hyperpyrexia syndrome, psychosis, psychotic disorder, reactive psychosis, rebound psychosis, rebound tachycardia, sedation, sensory disturbance, somnolence, stupor, substance abuse, substance abuse psychotic disorder, substance abuser, substance dependence, substance-induced mood disorder, substance-induced psychotic disorder, thinking abnormal, thought withdrawal, withdrawal hypertension, withdrawal syndrome

[a] There is no MedDRA PT for "hedonistic hemostatic dysregulation" listed in the pre-NDA Meeting Minutes, page 5, FDA Response to Question 4b, Item 5 (October 2016) and it was included in the list of MedDRA PT for completeness.

References

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