16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plans

Statistical Analysis Plan version 1.0 dated 22 December 2015

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16.1.9.2 Method for Analysis of Abuse Related Adverse Events

Abuse Assessment Section Terms

Statistical Analysis Plan

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Statistical Analysis Plan

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

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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
BMI	Body Mass Index
BMS	Biomedical Systems
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
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
Hb	hemoglobin
HR	Heart Rate

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Abbreviation	Description
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LD	Levodopa
LS	least square
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
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
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

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Abbreviation	Description
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

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 database lock. However, because this is an open-label study, the analyses defined after the first patient has been randomized to the study 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 it's 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.

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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

- To characterize the pulmonary safety, as assessed by spirometry (FEV1, FVC and FEV1/FVC ratio), over a 12-month period in the observational ('standard of care') cohort.

- To estimate the difference between the CVT-301-treated patients and the observational cohort on measures of pulmonary safety.

- To characterize the effects of CVT-301 on safety over a 12-month period: safety will be assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

- To evaluate the effect of CVT-301 on mean change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Q32-35] and wearing off [Q36-39]) measured at baseline and at 6 and 12 months after the initiation of CVT-301 treatment.

- To characterize the occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic over a 12-month period.

- To describe the effects of CVT-301 on Carbon Monoxide Diffusion Capacity (DLco) over a 12-month period.

3.3. EXPLORATORY EFFICACY OBJECTIVES

The following exploratory objectives related to the efficacy endpoints will primarily be assessed for the CVT-301-treated patients. The same objectives will be explored for the pool of CVT-301-naïve patients and patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies, if feasible.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode.
- Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively
- Change from pre-dose in the average UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode.
- Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10, 20, 30, and 60 minutes.
- Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic, maintaining the ON state at 60 minutes after study drug administration (per the examiner's subjective assessment).
- 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 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.
- Change from baseline in Schwab and England (S&E) Activities of Daily Living (ADL).
- Change from baseline in UPDRS Part 2 score.

3.4. PATIENT SELECTION

The study population for this study is PD patients experiencing motor fluctuations (OFF episodes) that meet the following inclusion criteria and do not meet any of the following exclusion criteria.

Patients may have been previously enrolled in the CVT-301-002 or CVT-301-003 studies, or may be CVT-301-naïve i.e. no previous exposure to CVT-301. Patients previously enrolled in the CVT-301-002 and CVT-301-003 studies must have completed all of the CVT-301 study visits without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from either of the CVT-301 studies prior to completion, for any reason, will not be eligible.

3.4.1. Inclusion Criteria

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 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
- Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the UK Brain Bank criteria, diagnosed after the age of 30 years.
- Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
- Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.
- Patients who are on a LD-containing therapy, not including Rytary (or equivalent), must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/dopamine decarboxylase inhibitor (DDI)-containing regimen.
- Patients who are on a LD containing therapy, when including Rytary (or equivalent), should be on a stable dose for at least 6 weeks prior to SV1
- The frequency of L-dopa administrations must be at least 3 times during the waking day and a total daily LD dose of ≤1600 mg (exclusive of PRN LD-containing medications).
- Patients should be stable on other PD medications for at least 4 weeks prior to SV1.

- Patients must have a ≥ 25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.

- Patients must have normal cognition as confirmed by a score of ≥ 25 on the MMSE.

- Patients must be able to perform a spirometry maneuver in the ON and OFF states, and must have a screening FEV1 ≥ 50% of predicted and an FEV1/FVC ratio >60% in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥ 50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine potential eligibility. All CVT-301-naïve patients with an FEV1/FVC ratio of >60% to <70% will be required to undergo a bronchodilator challenge and the results must be reviewed prior to entry into the study. Patients with an FEV1/FVC ratio that is >60% to <70% will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/European Respiratory Society [ERS] criteria prior to randomization. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization.)

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 deep brain stimulation [DBS] or cell transplantation).

- Patients with a history of psychotic symptoms requiring treatment, or suicide ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of anti-depressant and certain low-dose atypical antipsychotic medications are permitted, in case they are indicated to treat symptoms other than psychotic symptoms).

- Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
- Patients taking certain prohibited medications (see Section 9.4.2).
- Patients with a history of drug or alcohol abuse within the prior 12 months.
- Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years.
- Patients with any contraindication to performing routine spirometry or who are unable to perform a spirometry maneuver (see Appendix 20 for a list of contraindications).
- Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment.
- Patients with any condition that in the investigator's opinion would make patients unsuitable or interfere with their participation in the study. Potential issues of concern should be raised to the medical monitor during eligibility review.
- Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety.
- Patients who have been treated with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the beginning of the screening period (this includes investigational formulations of marketed products).
- Prior exposure to CVT-301.

3.5. DETERMINATION OF SAMPLE SIZE

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

The primary objective of this study will be to characterize the pulmonary safety within the CVT-301-treated patients and the differences between the groups will be estimated as a secondary objective. However, for the secondary comparison of FEV1 change

between the CVT-301 treatment group and the randomized observational cohort, the standard deviation of FEV1 change from baseline is expected to be 0.281 L, [redacted]. Assuming that there is no difference in the changes from baseline between the CVT-301-treated patients and the observational cohort, the study has the following power for the comparison between the 2 groups. The upper limit of the 95% confidence interval for the difference between the 2 groups in change from baseline in FEV1 will be less than 0.121 L with 90% power, assuming 188 and 86 patients completing the study in the CVT-301 treatment group and observational cohort, respectively. The sample size calculation was performed using nQuery Advisor, Version 7.0.

3.6. TREATMENT ASSIGNMENT & BLINDING

This study is a 12-month, open-label, randomized, multicenter study which will evaluate the safety and effects of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes) and will include a concurrent observational cohort of PD patients managed using the usual standards of care. Patients may have been previously enrolled in the CVT-301-002 or CVT-301-003 studies, or may be CVT-301-naïve. Patients who were previously enrolled in the CVT-301-002 and CVT-301-003 studies will be assigned to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD fine particle dose [FPD]), in this study. Patients who are CVT-301-naïve will be randomized in a 2:1 ratio to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD FPD) or the observational cohort. Randomization will be stratified by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%).

Following completion of SV2 and prior to randomization, the patients' eligibility criteria will be reviewed by delegated staff. Upon confirmation of eligibility, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). The study is an open-label study, so patients and clinical staff will not be blinded to study group assignment.

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.

Since this is an open-label study, 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 not blinded to the inhaled study treatment.

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 reinhaled, T0 is at the end of the reinhalation administration.

During the treatment period, patients will self-administer inhaled study treatment (CVT-301 DL1, 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. For each patient, the planned treatment period will be approximately 52 weeks, and maximum anticipated study duration, including screening and follow-up, will be approximately 62 weeks.

The screening period, which takes place within 35 days prior to Day 1 of the treatment period, will have 2 separate visits: SV1 and SV2 must be separated by at least 4 days. The screening period may be extended an additional 7 days if repeat screening assessments are required.

Before patients return to the clinic for TV/OV1, they will be randomized to treatment. 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 TV/OV1. The subsequent visits during the treatment period take place as follows:

- TV/OV2: Week 4; 28±5 days after TV/OV1.
- TV/OV3: Week 12; 84±14 days after TV/OV1.
- TV/OV4: Week 24; 168±14 days after TV/OV1.
- TV/OV5: Week 36; 252±14 days after TV/OV1.
- TV/OV6: Week 52; 364±14 days after TV/OV1.

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Patients who terminate the study early will complete TV/OV6 and return for the Follow-up DLco visit 4-5 weeks after TV/OV6.

Refer to Protocol Appendices 1 to 15 for tables of study assessments at each visit.

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	SV1		SV2		TV/OV1	TV/OV2	TV/OV3	TV/OV4	TV/OV5	TV/OV6
In Clinic Assessments	ON	OFF	ON	OFF	ON*	ON	ON	ON	ON	ON
MMSE	x									
UPDRS Part 1										
UPDRS Part 2					x			x		x
UPDRS Part 3	x	x				x**	x**	x**	x**	x**
UPDRS Part 4					x			x***		x***
C-SSRS					x	x	x	x	x	x
Epworth Sleep Scale					x			x		x
QUIP					x			x		x
PDQ-39					x			x		x
PGI-C								x***		x***
S&E ADL					x			x		x
At home for patients										
PD Diary (only treatment after screening)	x	x	x	x	x	x	x	x	x	x
ON/OFF logs (both groups)	x	x								
Inhaled dosing (CVT-301 only)					x	x	x	x	x	x

* For the CVT 301 arm these assessments are performed pre-dose

** Performed pre-dose, 10, 20, 30, and 60 min post dose (only performed in CVT 301 arm)

*** CVT 301 arm only

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 (TV/OV1) for each variable will be calculated at each subsequent visit.

Percent Predicted = 100 * (Observed) / Predicted, where predicted is calculated and provided to INC by Biomedical Systems (BMS).

4.2. SECONDARY ENDPOINTS

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

- Standard safety endpoints; for definitions see Section 8 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)

- Change from TV/OV1 (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.

- 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.

- Carbon Monoxide Diffusion Capacity (DLco) assessed over a 12 month period within the CVT 301 treated and the observational ('standard of care') cohorts. Variables will include the absolute DLco values and DLco expressed as % of predicted value.

4.3. EXPLORATORY EFFICACY ENDPOINTS

The following endpoints related to the exploratory efficacy objectives will be calculated.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode.
    - The UPDRS Part 3 total score will be calculated as the sum of the individual items of the UPDRS Part 3 questionnaire (UPDRS items 18-31) separately at each time point, i.e. the scores will range from 0 to 108. Missing individual items will be imputed using the 2 non-missing values at time points adjacent to the missing item on the same date. The maximum of the 2 adjacent values will be assigned as the score for the missing item. However, pre-dose values will not be assigned as post-dose values and if one of the adjacent values for a post-dose value is a pre-dose value, only 1 adjacent value will be used. The total score for UPDRS Part 3 assessments will be calculated after imputation of the missing item(s). Missing items at screening will not be imputed. If a pre-dose value is missing, the pre-dose value at the prior visit will be used. A missing TV/OV1 pre-dose value will be imputed using the last screening value in OFF state.

- Time curve of the UPDRS response shown as change from pre-dose in UPDRS Part 3 motor score to 10, 20, 30 and 60 minutes following treatment of patients experiencing an OFF episode in the clinic. The UPDRS Part 3 scores will be derived as described above.

- Change from pre-dose in the average UPDRS Part 3 score at 10 to 60 minutes following treatment of patients experiencing an OFF episode in the clinic. The change from pre-dose to the average of the 4 UPDRS Part 3 total scores (assessments scheduled at 10, 20, 30 and 60 minutes) will be used as the response variable in the statistical analysis.

- A ≥3, ≥6, and ≥11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes following treatment in the clinic (cumulative and non-cumulative). The non-missing UPDRS Part 3 motor scores at each time point (10, 20, 30 and 60 minutes post-dose) are classified as a reduction of ≥3 points or not, reduction of ≥6 points or not and reduction of ≥11 points or not. Furthermore,

for the purpose of the cumulative analysis, the time point (10, 20, 30 and 60 minutes post-dose) when the reduction of ≥3, ≥6 or ≥11 points occurs for the first time will be defined. The categorical scheduled time point is used in this analysis. The missing assessment regarding single items will be managed similarly as describe above. The missing values regarding visits will be managed by considering the missing visits as non-responses.

- 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 having missing data.

- Change from baseline (3 consecutive days prior to TV/OV1, or in case of missing data, the last 3 recorded days before TV/OV1) 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, total daily ON time with non-troublesome dyskinesia, and 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 TV/OV1 (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.

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- 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 TV/OV1 (baseline) Schwab and England (S&E) Activities of Daily Living (ADL). No further derivation will be done for the S&E scores.

- Change from TV/OV1 (baseline) 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.

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 randomized patients who received at least 1 dose of inhaled CVT-301 and patients from the Observational Cohort. Patients will be analyzed according to study treatment 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. Patients will be analyzed according to randomized treatment. The ITT Population will be used for all analyses of exploratory efficacy endpoints.

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.

The deviations will be classified during a review process with the Sponsor and other study personnel (as appropriate) before database lock. The deviations will be classified as minor or major with/without impact on pulmonary assessments during the review process. All decisions regarding major 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 following deviations will be identified, but do not necessarily represent a complete list of potential deviations:

- Administration of PD medications after the usual morning dose of PD medication and before study drug administration
- Incorrect study drug administered at a visit
- Drug non-compliance including but not limited to unapproved dose modification

- Failure to return for defined study visits or within an acceptable visit window for completion of study assessments

The number of subjects with minor, major with/without impact on pulmonary assessments protocol deviations will be summarized by treatment groups and overall. All protocol deviations will be listed.

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 Patient ID (and by visit and by time point, if applicable), unless specified otherwise.

All applicable data will be summarized by treatment group (Observational Cohort or CVT-301) and overall in tables, unless specified otherwise. The CVT-301 group will be broken down into CVT-301-naïve patients and patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies. 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.

For the Observational Cohort, the "start of treatment" will be defined as attendance of TV/OV1, unless specified otherwise. Baseline will be defined as the assessments performed at TV/OV1. In case of missing data, the last non-missing screening assessment will be used as the baseline value.

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 UPDRS and other exploratory 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 percents. The total number of patients in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise in the table shell. All percents will be presented with one decimal point, unless specified otherwise. Percents equal to 100 will be presented as 100% and percents 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.

6.2. KEY DEFINITIONS

Age

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

Age = int ((date of informed consent- 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) =
Date of Screening Visit 1 (M/Y) - Date of diagnosis (M/Y)

Duration of levodopa treatment (months) =
Date of Screening Visit 1 (M/Y) - Start date of levodopa treatment (M/Y)

Time since onset of wearing off episodes (months) =
Date of Screening Visit 1 (M/Y) - Date of onset of wearing off episodes (M/Y)

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 =

Statistical Analysis Plan

(Post-dose value – Pre-dose value)*100/Pre-dose value

Baseline

For CVT-301 patients, baseline is defined as the last non-missing assessment before the first dose of study drug, unless specified otherwise. For the Observational Cohort, baseline is defined as TV/OV1, or, in the case of missing data, the last non-missing assessment before TV/OV1, unless specified otherwise. However, for all patients who were included in the CVT 301-002 or CVT-301-003 studies, TV/OV1 of the CVT-301-005 study will be used as baseline.

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 and DLCO predicted, adjusted for hemoglobin (Hb)

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 in)*
- *Women predicted DLCO = 2.2382 - (0.1111 x age) + (0.4068 x height in)*

Where age is the age at the time of assessment taken, 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 observed value is the value provided by TechEd, and the predicted value is the predicted value that provided by BMS and is the values closest to the date of observed value taken. The details are listed in table below.

$DLCO_{predicted}$, percent predicted of FEV1 and FVC	Value selection for Hb, predicted FEV1 and FVC
Screening (prior to randomization)	From TV/OV1 or the value closest to the date of DLCO assessment if the value at TV/OV1 is missing
TV/OV3, within 2 weeks prior to 3	From TV/OV3 or the value closest to the date of DLCO assessment if the value at TV/OV3 is missing
TV/OV4, within 2 weeks prior to 6	From TV/OV4 or the value closest to the date of DLCO assessment if the value at TV/OV4 is missing
TV/OV5, within 2 weeks prior to 9	From TV/OV5 or the value closest to the date of DLCO assessment if the value at TV/OV5 is missing
TV/OV6, within 2 weeks prior to 12	From TV/OV6 or the value closest to the date of DLCO assessment if the value at TV/OV6 is missing
4 to 5 weeks after TV/OV6	The latest non-missing Hb that closest to the date of DLCO assessment taken.

6.3. MISSING DATA

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

- For calculation of the UPDRS part 3 scores, the missing single UPDRS items will be imputed as described in Section 4.3.

- For the primary analysis of spirometry and selected explorative 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 8.1.

- 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 9.1.

- 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 8.4.

The Safety and ITT populations will be used for the analysis of the primary, secondary and exploratory endpoints. 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.

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 Early Termination (ET) visit (PDQ-39, UPDRS Part 2, UPDRS Part 4, S&E ADL score and safety assessments). CVT 301 treated patients will also perform the UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post dose as well as the PGI-C. The following rules will be used to analyze the data collected at the ET visit:

- For the PDQ-39, PGI-C, UPDRS Part 2, UPDRS Part 3, UPDRS Part 4 and S&E ADL score, the data from the ET visit will be re-assigned to TV/OV6 in case there is no TV/OV6 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 efficacy endpoints (at least the Change from pre-dose in UPDRS Part 3 motor score at 30 minutes post-dose and the mean 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 TV/OV1 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 TV/OV1 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 TV/OV1 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. The percentages will be calculated based on the number of randomized patients, unless otherwise specified). The randomized set will include all randomized patients as well as those from CVT-301-002 and CVT-301-003 studies who were assigned to the CVT 301 treatment group.

- 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 randomized into the 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)
- 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 population by treatment group and overall. 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 TV/OV1 will be used as baseline. If the data are only available on 1 or 2 days prior to TV/OV1, the available data will be used as baseline. If there is no data prior to TV/OV1, 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 TV/OV1 will be used as baseline. If the data are only available on 1 or 2 days prior to TV/OV1, the available data will be used as baseline. If there is no data prior to TV/OV1, 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 TV/OV1)
- Proportion of patients with total daily OFF time <4.5 hours or ≥4.5 hours (from PD diary before TV/OV1)
- 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 TV/OV1, Non-dyskinetic before TV/OV1). 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 TV/OV1 versus non-dyskinetic; Patient with the baseline 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 TV/OV1 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, using the Safety population, will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

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 or TV/OV1 for the observational cohort will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications.

Tables will be generated for the Safety Population. 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. SAFETY

The population used for safety analyses will be the Safety Population. The analyses are outlined below.

8.1. SPIROMETRY

Spirometry will be performed by trained and qualified staff at each study site. 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.

FEV1, FVC, FEV1/FVC ratio and DLco will be summarized descriptively by treatment group and overall. For screening data, the summary will be presented for each motor status, ON or OFF, separately. For other visits, data in ON or OFF state will be combined for summary. The following will be summarized:

- Change from baseline to other visits Arrival values for each parameter. The baseline is defined as the TV/OV1 Arrival value. If the TV/OV1 Arrival value is missing, the last available value in ON state before the first dose of study drug will be used.
- 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 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 classified as not meeting the criteria for acceptability, not meeting the criteria for repeatability or as other/unknown and summarized.

The spirometry analyses will be repeated for the subset of assessments meeting the ATS quality criteria.

Another subset analysis will be performed by excluding the spirometry 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.

The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.

In addition to the descriptive statistics, the changes in the spirometry 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 or observational cohort), 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 between CVT-301 and observational cohort at each visit; along with the 95% confidence interval (CI) will be provided in a table. Treatment 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 avisit usubjid;
model chg=base pdsevbl fev1bl trta avisit trta*avisit / ddfm=kr;
repeated avisit / subject=usubjid(trtp) type=un;
lsmeans trtp*avisit / cl;
estimate 'CVT vs OBS Month 1'
        trta 1 -1 trta*avisit 1 0 0 0 0 -1 0 0 0 0 / cl;
estimate 'CVT vs OBS Month 3'
        trta 1 -1 trta*avisit 0 1 0 0 0 0 -1 0 0 0 / cl;
estimate 'CVT vs OBS Month 6'
        trta 1 -1 trta*avisit 0 0 1 0 0 0 0 -1 0 0 / cl;
estimate 'CVT vs OBS Month 9'
        trta 1 -1 trta*avisit 0 0 0 1 0 0 0 0 -1 0 / cl;
estimate 'CVT vs OBS Month 12'
        trta 1 -1 trta*avisit 0 0 0 0 1 0 0 0 0 -1 / cl;
run;
```

The Safety population will be used for the primary analysis.

Sensitivity analyses of the spirometry data

The following sensitivity analysis will be performed for the primary 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 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 arm 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, baseline spirometry value 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 model with treatment group, baseline spirometry value, 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 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 differences. Estimates and corresponding 95% confidence intervals will be calculated.

8.2. EXTENT OF EXPOSURE

The following information will be summarized for CVT-301 treated subjects:

- The number of patients with dose change
- Duration of exposure (days)
- Total exposure to study treatment, expressed as person years (sum of exposure to study treatment over all CVT – 301 treated patients)
- 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.

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.

8.3. 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.

8.4. 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 study drug. For the observational cohort, TEAE will

be defined as events that occur during/after TV/OV1. 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 overall total. TEAEs with onset after the treatment period are attributed to the treatment group and dose level 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 will be presented (number of TEAEs divided by the total exposure to CVT 301 or observation, 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.

8.5. LABORATORY EVALUATIONS

Laboratory samples for hematology and clinical chemistry will be analyzed by a central laboratory (located in the United Kingdom for EU sites and the United States for US sites) 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 handling 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	1	>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 visit 3 assessment. If the visit 3 assessment is missing, the last non-missing screening assessment will be used as baseline. * 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.

8.6. 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 for each parameter. The baseline is defined as the TV/OV1. If TV/OV1, the last non-missing screening assessment will be used as baseline.

- Actual values and change from pre-dose to post-dose time points at TV/OV1 by time point for each parameter for CVT-301 treated patients
- 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	2x	0.5x
Respiration Rate	brpm	>32	<8	1.5x	NA
Systolic Blood Pressure (supine)	mmHg	>200	<85	1.6x	0.2x
Diastolic Blood pressure (supine)	mmHg	>120	<40		0.2x
*Pre-dose values will be used for corresponding post-dose values assessment at TV/OV1. 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.

8.7. 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 for each parameter. The baseline is defined as the TV/OV1 value. If TV/OV1 value is missing, the last non-missing screening assessment will be used as baseline.
- 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

8.8. 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

8.9. 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 from baseline table will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.

8.10. 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 will be summarized by treatment group and overall (for handling of data from the ET visit, see Section 6.4).

8.11. 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.

The frequency and percentage of patients with positive response for each of the item within each section will be summarized by visit 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

8.12. UPDRS PART 4

Changes from baseline to the subsequent visits in UPDRS Part 4 sum scores (dyskinesia sum score, wearing-off sum score) will be analyzed using a similar MMRM as for the UPDRS Part 3 scores (described below) to estimate the within-group changes. Otherwise, the data will be presented with descriptive statistics only classified by visit for CVT treated patients. The observed cases will be used in the analysis and summaries.

8.13. 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. EXPLORATORY EFFICACY

9.1. EXPLORATORY EFFICACY ENDPOINT AND ANALYSIS

The ITT population will be used for the exploratory efficacy analysis. Patients will be analyzed according to randomized treatment. The within group changes from baseline in continuous efficacy variables will be estimated using an MMRM. No between group differences will be calculated, unless otherwise specified. The model will include visit and the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) as fixed factors. The baseline value will be used as a covariate. For variables which do not have a pretreatment baseline assessment, OFF-state baseline UPDRS Part 3 score will be used as the baseline covariate. An unstructured covariance structure will be applied for the MMRM. In case the model will not converge with the unstructured covariance structure, compound symmetry will be used instead. For all patients, categorical data will be evaluated descriptively. Each visit will be evaluated separately for the categorical endpoints. The exploratory efficacy endpoints and associated analyses are as follows. For the detailed definition of the endpoints, see Section 4.3.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes and the average of the motor score at 10-60 following treatment of patients experiencing an OFF episode in the clinic. Change from pre-dose in the average UPDRS Part 3 score at 10 to 60 minutes is calculated as the mean of change of UPDRS Part III total score from pre-dose to each time point post-dose if UPDRS Part III total score is available for at least 2 time points post-dose. The scheduled post-dose UPDRS Part III assessments are at 10, 20, 30, 60 minutes post-dose, respectively. If there is more than 2 time points post-dose with missing UPDRS Part III total score, the change of UPDRS Part III total score from pre-dose to 10 to 60 minutes post-dose will be missing. A MMRM model as defined above will be used.

- Time curve of the UPDRS response shown as change from pre-dose in UPDRS Part 3 motor score to 10, 20, 30 and 60 minutes following treatment of patients experiencing an OFF episode in the clinic. A separate MMRM model will be fitted for each of the time points.

- A ≥3, ≥6, and ≥11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes following treatment in the clinic (cumulative and non-cumulative). For the non-cumulative analysis, the proportions of patients with a reduction will be tabulated by treatment group, visit and time point. For the cumulative analysis, the cumulative proportions of patients who achieved the first reduction before or at the time point in question will be tabulated by visit and time point.

- 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.

- Change from baseline (3 consecutive days prior to TV/OV1) 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. However, the baseline daily OFF time will be used as a covariate in the MMRM model instead of the OFF-state baseline UPDRS part 3 score. 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.

- 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.

- Changes from TV/OV1 in endpoints based on S&E ADL score, UPDRS Part 2 score, and PDQ-39 sub-scores. An ANCOVA model with the treatment group and stratification variables as fixed factors and the TV/OV1 value as a covariate will be used to estimate the treatment differences. Otherwise, the data will be presented with descriptive statistics only classified by treatment group and visit. The observed cases will be used in the analysis and summaries.

Sensitivity analyses of the exploratory efficacy data

The following sensitivity analysis will be performed for the UPDRS Part 3 motor scores at 30 minutes post-dose and daily OFF time exploratory efficacy endpoints.

- 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 arm 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 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 spirometry value, 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.

10. INTERIM ANALYSES

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

Data summary, which will not affect study conduct, may be prepared to support regulatory submission. These analyses will be described in the Interim Analysis Charter.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes from the analyses planned in the protocol.

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:

- 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 treatments in the tables will be Placebo first, followed by CVT-301 and a total 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
Minimum	XXX,
Maximum	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. 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.

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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Not Applicable.

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Number of Subjects Enrolled and Study Termination
(All Available Population)

	O.C. n (%)	CVT-301 002/003 n (%)	CVT-301 Naive n (%)	CVT-301 Total n (%)	Overall n (%)
Screened					xx
Failed Screening [a]					xx (xx.x)
Randomized [a]	xx	xx	xx	xx	xx (xx.x)
Safety Population [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ITT Population [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Study [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawn from Study [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Withdrawal from Study [c]					
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Withdrew Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naive is for the CVT-301 naive patients.
[a] Percentages are based on the number of screened subjects.
[b] Percentages are based on the number of randomized subjects.
[c] Percentages are based on the number of randomized and dosed subjects withdrawn from study.
[d] Percentages are based on the number of subjects in safety population.
Cross-reference: Listing 16.2.1, 16.2.3.3

Table 14.1.1.2
Number of Subjects in Each Population by Study Center
All Subjects

	O.C.			002/003			Naive		
	Randomized n (%)	Safety n (%)	ITT n (%)	Randomized n (%)	Safety n (%)	ITT n (%)	Randomized n (%)	Safety n (%)	ITT n (%)
Overall	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Site 1	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
Site 2	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
Site 3	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
…	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. PP=Per-protocol; Percentages are based on the number of subjects in each population for each treatment group.

Cross-reference: Listing 16.2.1, 16.2.3.3

Table 14.1.1.2
Number of Subjects in Each Population by Study Center
All Subjects

	CVT-301 Total			Overall		
	Randomized n (%)	Safety n (%)	ITT n (%)	Randomized n (%)	Safety n (%)	ITT n (%)
Overall	xxx	xxx	xxx	xxx	xxx	xxx
Site 1	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
Site 2	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
Site 3	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)
…	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)	xxx(xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. PP=Per-protocol; Percentages are based on the number of subjects in each population for each treatment group.

Cross-reference: Listing 16.2.1, 16.2.3.3

Table 14.1.2.1
Summary of Protocol Deviation
Randomized Set

	O. C. N=xxx n (%)	CVT-301 002/003 N=xxx n (%)	CVT-301 Naive N=xxx n (%)	CVT-301 Total N=xxx n (%)	Overall N=xxx n (%)
Any Protocol Deviation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any Minor Protocol Deviation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any Major Protocol Deviation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Without Impact on Pulmonary Assessments	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
With Pulmonary Impact on Assessments	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on the number of subjects in each treatment group.
Cross-reference: Appendix 16.2.2.1

Program Name: Lxxxxx.sas
Table Generation: ddmonyyyy hh:mm

Table 14.1.3.1.1
Demographic and Baseline Characteristics
(Safety Population)

Characteristic	Statistic	O. C. (N=xx)	CVT-301 002/003 (N=xx)	CVT-301 Naïve (N=xx)	CVT-301 Total (N=xx)	Overall (N=xx)
Age (years)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Age (years)						
<65	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=65	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gender						
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity						
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race						
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Weight (kg)	...					
BMI ((kg/m^2) [a]	...					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] BMI was calculated as weight (kg) / [height (m)]^2.
Cross-reference: Listing 16.2.4.1, 16.2.4.4, 16.2.4.7, 16.2.4.10

Table 14.1.3.1.1
Demographic and Baseline Characteristics
(**Safety Population**)

Characteristic	Statistic	O. C. (N=xx)	CVT-301 002/003 (N=xx)	CVT-301 Naïve (N=xx)	CVT-301 Total (N=xx)	Overall (N=xx)
Country						
United States	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Canada	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...						
Smoking History						
Never	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Current	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Years Smoked	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Number of Cigarettes/Day	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	…					
MMSE Total Score	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	…					
Screening Spirometry						
FEV1 <60% or FEV1/FVC ratio <70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FEV1 >=60% and FEV1/FVC ratio >=70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline PD Severity						
Hoehn & Yahr scale < 2.5 points	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hoehn & Yahr scale>= 2.5 points	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomization Strata						
Hoehn & Yahr scale < 2.5 points AND FEV1 <60% or FEV1/FVC ratio <70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hoehn & Yahr scale < 2.5 points AND FEV1 >=60% and FEV1/FVC ratio >=70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hoehn & Yahr scale>= 2.5 points AND FEV1 <60% or FEV1/FVC ratio <70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hoehn & Yahr scale>= 2.5 points AND FEV1 >=60% and FEV1/FVC ratio >=70%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] BMI was calculated as weight (kg) / [height (m)]^2.
Cross-reference: Listing 16.2.4.1, 16.2.4.4, 16.2.4.7, 16.2.4.10

Table 14.1.3.1.2
Demographic and Baseline Characteristics
(ITT Population)

Table 14.1.3.1.3
Demographic and Baseline Characteristics
by Baseline PD Severity
(ITT Population)

will have similar format as Table 14.1.2.1. Summarize for "Hoehn & Yahr scale < 2.5 points" and "Hoehn & Yahr scale >= 2.5 points" respectively.

Table 14.1.3.1.4
Demographic and Baseline Characteristics
by Baseline Dyskinesia
(ITT Population)

will have similar format as Table 14.1.2.1. Summarize for "Dyskinetic before TV1" and "Non-dyskinetic before TV1" respectively.

Table 14.1.3.1.5
Demographic and Baseline Characteristics
by Baseline Daily Levodopa Dose
(ITT Population)

will have similar format as Table 14.1.2.1. Summarize for "**Baseline Daily Levodopa Dose**<=Median of **Baseline Daily Levodopa Dose**" and "**Baseline Daily Levodopa Dose**>=Median of **Baseline Daily Levodopa Dose**" respectively.

Table 14.1.3.1.6
Demographic and Baseline Characteristics
by PD Diary Mean Daily OFF Time during Screening
(ITT Population)

will have similar format as Table 14.1.2.1. Summarize for "PD Diary Mean Daily OFF Time during Screening < 4.5 Hours" and "PD Diary Mean Daily OFF Time during Screening >=4.5 Hours" respectively.

Table 14.1.3.1.7
Demographic and Baseline Characteristics
by Screening Spirometry
(ITT Population)

will have similar format as Table 14.1.2.1. Summarize for "FEV1 <60% or FEV1/FVC ratio <70%" and "FEV1 ≥60% and FEV1/FVC ratio ≥70%" respectively.

Table 14.1.3.1.8
Demographic and Baseline Characteristics
by Age Group
(ITT Population)

will have similar format as Table 14.1.3.1.1 Summarize for "Non-elderly (<65 years)" and "Elderly (≥65 years) patients" respectively.

Table 14.1.3.1.9
Demographic and Baseline Characteristics
by Gender
(ITT Population)

will have similar format as Table 14.1.3.1.1 Summarize for “Female” and “Male” respectively.

Table 14.1.3.2.1
Parkinson's Disease History
(Safety Population)

			CVT-301			
	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naïve (N=xx)	Total (N=xx)	Overall (N=xx)
Time Since Diagnosis of Parkinson's Disease (months)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Duration of Levodopa Treatment (months)	...					
Duration since Onset of Fluctuation (Wearing Off) Episodes (months)	...					
Baseline Average Daily Levodopa Dose (mg)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Baseline Average # of Daily Levodopa Doses	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Screening UPDRS III Total Score (ON State)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Screening UPDRS III Total Score (OFF State)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Difference from OFF to ON State in Screening UPDRS III Total Score	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Percent Difference from OFF to ON in Screening UPDRS III Total Score (%)[a]	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
Average Number of Daily OFF Episodes Experienced	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
Patients who Changed the Timing of Their Usual Levodopa Medication	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patients who Took an Extra Dose of Levodopa or other PD Medication	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] % was calculated as OFF-ON/OFF * 100%'.
[b]The patients who have recorded at least 1 hour of dyskinesia (either ON with non-troublesome dyskinesia or ON with troublesome
Cross-reference: Listing 16.2.4.3, 16.2.4.8, 16.2.4.9, 16.2.5.3, 16.2.6.1.1, **16.2.8.2.4.1**

Table 14.1.3.2.1
Parkinson's Disease History
(Safety Population)

			CVT-301			
	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naïve (N=xx)	Total (N=xx)	Overall (N=xx)
Screening PD Diary						
Mean Daily OFF Time (hours)	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	…					
Mean Daily OFF Time during Screening< 4.5 Hours	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean Daily OFF Time during Screening>= 4.5 Hours	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mean Daily ON Time Without Dyskinesia (hours)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Mean Daily ON Time With Non-troublesome Dyskinesia (hours)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Mean Daily ON Time With Troublesome Dyskinesia (hours)	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
Baseline Dyskinesia						
Dyskinetic before TV1/OV1[b]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-dyskinetic before TV1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screening Spirometry data (ON)						
FEV1	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
	...					
FVC	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
FEV1/FVC	n	xx	xx	xx	xx	xx
	mean	xx.x	xx.x	xx.x	xx.x	xx.x
Screening Spirometry data (OFF)						
FEV1						
FVC						
FEV1/FVC						

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] % was calculated as OFF-ON/OFF * 100%.
[b]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/OV1 will be classified as dyskinetic.

Cross-reference: Listing 16.2.4.3, 16.2.4.8, 16.2.4.9, 16.2.5.3, 16.2.6.1.1, **16.2.8.2.4.1**

Table 14.1.3.2.2
Parkinson's Disease History
(ITT Population)

will have similar format as Table 14.1.3.2.1.

Table 14.1.3.2.3
Parkinson's Disease History
by Baseline PD Severity
(ITT Population)

will have similar format as Table 14.1.3.2.1, but to summarize for "Hoehn & Yahr scale < 2.5 points" and "Hoehn & Yahr scale >= 2.5 points" respectively. No need to summarize "Baseline PD Severity".

Table 14.1.3.2.4
Parkinson's Disease History
by Baseline Dyskinesia
(ITT Population)

will have similar format as Table 14.1.3.2.1, but to summarize for "Dyskinetic before Visit 3" and "Non-dyskinetic before Visit 3" respectively. No need to summarize "Baseline Dyskinesia".

Table 14.1.3.2.5
Parkinson's Disease History
by Baseline Daily Levodopa Dose
(ITT Population)

will have similar format as Table 14.1.3.2.1. Summarize for "**Baseline Daily Levodopa Dose**<=Median of **Baseline Daily Levodopa Dose**" and "**Baseline Daily Levodopa Dose**>=Median of **Baseline Daily Levodopa Dose** " respectively.

Table 14.1.3.2.6
Parkinson's Disease History
by PD Diary Mean Daily OFF Time during Screening
(ITT Population)

will have similar format as Table 14.1.3.2.11, but to summarize for *"PD Diary Mean Daily OFF Time during Screening <4.5 Hours" and "PD Diary Mean Daily OFF Time during Screening >=4.5 Hours".*

Table 14.1.3.2.7
Parkinson's Disease History
by Screening Spirometry
(ITT Population)

will have similar format as Table 14.1.3.2.1. Summarize for "FEV1 <60% or FEV1/FVC ratio <70%" and "FEV1 ≥60% and FEV1/FVC ratio ≥70%" respectively.

Table 14.1.3.2.8
Parkinson's Disease History
by Age Group
(ITT Population)

will have similar format as Table 14.1.3.2.1. Summarize for "Non-elderly (<65 years)" and "Elderly (≥65 years) patients" respectively.

Table 14.1.3.2.9
Parkinson's Disease History
by Gender
(ITT Population)

will have similar format as Table 14.1.3.2.1. Summarize for "Female" and "Male" respectively.

Table 14.1.3.2.10
Modified Hoehn and Yahr Staging in "ON" State
(Safety Population)

	O. C. (N=xx) n (%)	CVT-301 002/003 (N=xx) n (%)	CVT-301 Naive (N=xx) n (%)	CVT-301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Modified Hoehn and Yahr					
Stage 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 1.5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 2.5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Stage 5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Cross-reference: Listing 16.2.4.6

Table 14.1.3.2.11
Modified Hoehn and Yahr Staging in "ON" State
(ITT Population)

will have similar format as Table 14.1.3.2.11.

Table 14.1.3.2.12
Distribution of Average Daily OFF Time at Baseline
(Safety Population)

Time Interval/OFF Hours (%)	O. C. (N=xx)	CVT-301 002/003 (N=xx)	CVT-301 Naive (N=xx)	CVT-301 Total (N=xx)	Overall (N=xx)
Average Total Daily OFF Time (Hours)	xx.x	xx.x	xx.x	xx.x	xx.x
Average Daily OFF Hours (%)					
00:00 -< 00:30	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
00:30 -< 01:00	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
01:00 -< 01:30	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
01:30 -< 02:00	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
...					
Continue with 30 mins interval until 23:30 -< 24:00					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Total daily OFF time is calculated as the average of total OFF time collected three days prior to TV1/OV1and is normalized to 16 awake hours per day. Average daily OFF Hours at each interval will be calculated similarly. The percentage is based on Total Daily OFF Time.
Cross-reference: Listing 16.2.6.2.2

Table 14.1.3.2.13
Distribution of Cumulative Average Daily OFF Time at Baseline
(Safety Population)

Time Interval/OFF Hours (%)	O. C. (N=xx)	CVT-301 002/003 (N=xx)	CVT-301 Naive (N=xx)	CVT-301 Total (N=xx)	Overall (N=xx)
Average Total Daily OFF Time (Hours)	xx.x	xx.x	xx.x	xx.x	xx.x
Cumulative Average Daily OFF Hours (%)					
00:00 -< 00:30	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
00:00 -< 01:00	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
00:00 -< 01:30	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
00:00 -< 02:00	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
...					
Continue with 30 mins interval until 00:00 -< 24:00					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Total daily OFF time is calculated as the average of total OFF time collected three days prior to TV1/OV1and is normalized to 16 awake hours per day. Cumulative Average daily OFF Hours are calculated similarly. The percentage is based on Total Daily OFF Time.
Cross-reference: Listing 16.2.6.2.2

Table 14.1.3.3
Medical History
(Safety Population)

System Organ Class Preferred Term [a]	O. C. (N=xx) Subjects n (%)	Events n	CVT-301 002/003 (N=xx) Subjects n (%)	Events n	CVT-301 Naïve (N=xx) Subjects n (%)	Events n	CVT-301 Total (N=xx) Subjects n (%)	Events n	Overall (N=xx) Subjects n (%)	Events n
Any Medical History	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] Medical history data were coded into system organ class and preferred term by using MedDRA version 17.0.

Cross-reference: Listing 16.2.4.2

Programming note: The table will be sorted by total descending frequency of SOC and then, within a SOC, by total descending frequency of PT.

Table 14.1.4.1
Prior Medications
(Safety Population)

ATC Level 1 ATC Level 2 Preferred Term [a]	O. C. (N=xx) Subjects n (%)	Meds n	CVT-301 002/003 (N=xx) Subjects n (%)	Meds n	CVT-301 Naive (N=xx) Subjects n (%)	Meds n	CVT-301 Total (N=xx) Subjects n (%)	Medi n	Overall (N=xx) Subjects n (%)	Meds n
Any Medications	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: Meds = Medications; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Data from "Prior and Concomitant Medications" CRF page were summarized in this table. The medications with a stop date before the first date of study drug dosing will be considered prior medications.
[a] Medications were coded into ATC and preferred term using the WHO Drug Dictionary,Q1March2014.

Cross-reference: Listing 16.2.4.11.1

Programming note: The table will be sorted by total descending frequency of ATC1 and ATC2 and then, within a ATC2, by total descending frequency of PT.

Table 14.1.4.2
Concomitant Medications
(Safety Population)

Will have same format as Table 14.1.4.1

Note: Meds = Medications; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Data from "Prior and Concomitant Medications" CRF page were summarized in this table. The medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications.
[a] Medications were coded into ATC and preferred term using the WHO Drug Dictionary, Q1March2014.

Cross-reference: Listing 16.2.4.11.2

Table 14.1.4.3
Parkinson's disease Treatment Medications at Baseline
(ITT Population)

			CVT-301							
ATC Level 4	O. C. (N=xx)		002/003 (N=xx)		Naive (N=xx)		Total (N=xx)		Overall (N=xx)	
Preferred Term	Subjects	Meds	Subjects	Meds	Subjects	Meds	Subjects	Meds	Subjects	Meds
[a]	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Any Medications	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 4	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 4	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 4	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
ATC Level 4	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
...	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: Meds = Medications; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] Medications were coded into ATC and preferred term using the WHO Drug Dictionary, Q1March2014.The medications which start with ATC code N04 are considered as baseline PD treatment medications.
Cross-reference: Listing 16.2.4.11.2

Programming note: The table will be sorted by total descending frequency of ATC and then, within a ATC, by total descending frequency of PT.

Table 14.2.1.1
Exploratory Efficacy Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 10 Minutes Post-dose by Visit
(ITT Population)

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 10 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.1.2

Table 14.2.1.2
Exploratory Efficacy Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 20 Minutes Post-dose by Visit
(ITT Population)

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 20 minutes at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit ((TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.1.2

Table 14.2.1.3.1
Exploratory Efficacy Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit
(ITT Population)

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.1.2

will have similar format as Table 14.2.1.1.1.

Table 14.2.1.3.2
Sensitivity Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit
MI analysis with Missing At Random Assumption
(ITT Population)

Visit/Statistic((Number of Datasets = 100)	CVT-301 (N=xx)
TV2	
MI Mean (SE)	xx.x(xx.xx)
MI Median	xx.x
MI Minimum, MI Maximum	xx, xx
TV3	
TV4	
TV5	
TV6	
TV3	

Note: TV = Treatment Visit;
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing at random. MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate at each visi
Cross-reference: Listing 16.2.6.1.2

Table 14.2.1.3.3
Subgroup Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Baseline PD Severity
(ITT Population)

Hoehn & Yahr scale < 2.5 points

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variable (screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for "Hoehn & Yahr scale < 2.5 points" *and* "Hoehn & Yahr scale >= 2.5 points"*, and do not include baseline PD severity in MMRM model.*

Table 14.2.1.3.4
Exploratory Efficacy Subgroup Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Baseline Dyskinesia
(ITT Population)

Dyskinetic before TV1

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for Dyskinetic before TV1/OV1*versus Non*-Dyskinetic before TV1

Table 14.2.1.3.5
Exploratory Efficacy Subgroup Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Baseline Daily Levodopa Dose
(ITT Population)

Baseline Daily Levodopa Dose<=Median of **Baseline Daily Levodopa Dose**

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for "**Baseline Daily Levodopa Dose**<=Median of **Baseline Daily Levodopa Dose**" and "**Baseline Daily Levodopa Dose**>=Median of **Baseline Daily Levodopa Dose**" respectively.

Table 14.2.1.3.6
Exploratory Efficacy Subgroup Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by PD Diary Mean Daily OFF Time during Screening
(ITT Population)

PD Diary Mean Daily OFF Time during Screening <4.5 Hours

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for "PD Diary Mean Daily OFF Time during Screening<4.5 Hours" and "PD Diary Mean Daily OFF Time during Screening>=4.5 Hours".

Table 14.2.1.3.7
Exploratory Efficacy Subgroup Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Screening Spirometry
(ITT Population)

FEV1 <60% or FEV1/FVC ratio <70%

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for FEV1 <60% or FEV1/FVC ratio <70% and FEV1 ≥60% and FEV1/FVC ratio ≥70%

Table 14.2.1.3.8
Exploratory Efficacy Subgroup Analysis: Mean Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Age Group
(ITT Population)

Non-elderly (<65 years)

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for 'Non-elderly (<65 years)' and 'Elderly (>=65 years)' respectively.

Table 14.2.1.3.9
Exploratory Efficacy Subgroup Analysis: Mean Change from Pre-dose in the UPDRS Part 3 Score at 30 Minutes Post-dose by Visit by Gender
(ITT Population)

Male

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV2	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV3			
TV4			
TV5			
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 30 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; the Baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.6.1.2

Programming Note: Do separate analysis for 'Male' and 'Female' respectively.

Table 14.2.1.4
Exploratory Efficacy Analysis: Change from Pre-dose in the UPDRS Part 3 Score at 60 Minutes Post-dose by Visit
(ITT Population)

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 total scores at 60 minutes at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.1.2

Table 14.2.1.5
Exploratory Efficacy Analysis: Change from Pre-dose in the Average UPDRS Part 3 Score at 10 to 60 Minutes Post-dose by Visit
(ITT Population)

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose to the average of the 4 post-dose UPDRS Part 3 total scores (10,20,30 and 60 minutes) at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.1.2

will have similar format as Table 14.2.1.1.1.

Table 14.2.2.1
Exploratory Efficacy Analysis: Change from Pre-dose in UPDRS Part 3 Score to 10, 20, 30, 60 minutes Post-dose by Visit
(ITT Population)

Timeponit	Visit	Statistic	CVT-301 (N=xx)	p-value
10 mins Post-dose	Overall	Overall p-value		
		Baseline Hoehn and Yahr stage		0.xxx
		Screening Spirometry		0.xxx
		Treatment		0.xxx
		Visit		0.xxx
		Baseline UPDRS Part 3 Score		0.xxx
	TV2	n	xx	
		LS Mean	xx.x	
		SE (LS Mean)	xx.xx	
		95% CI (LS Mean)	(xx.x, xx.x)	
	TV3	...		
	TV4	...		
	TV5			
	TV6			
20 mins Post-dose		...		
30 mins Post-dose		...		
60 mins Post-dose		...		

Note: TV = Treatment Visit;
MMRM model uses the change from pre-dose in UPDRS Part 3 score to 10, 20, 30, or 60 minutes at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes visit (TV2, TV3, TV4, TV5, TV6) the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; baseline UPDRS part 3 score will be included as a covariate, assuming an unstructured covariance matrix. A separate MMRM model will be fitted for each of the time points.

Cross-reference: Listing 16.2.6.1.2

Table 14.2.2.2
Exploratory Efficacy Analysis: Change from Pre-Dose to 10, 20, 30, 60 minutes Post-dose in UPDRS Part 3 Score by Visit and Timepoint
(ITT Population)

Timepoint	Visit	Statistic	CVT-301 (N=xx)
Pre-dose	TV2	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
	TV3	...	
	TV4	...	
	…		
10 mins post-dose	TV2	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
		Change from Pre-dose	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
	TV3	...	
	TV4	...	
	…		
20 mins Post-dose			
30 mins Post-dose			
60 mins Post-dose			

Note: TV = Treatment Visit;
Cross-reference: Listing 16.2.6.1.2

Table 14.2.2.3
Exploratory Efficacy Analysis: **Change from Pre-Dose to 10, 20, 30, 60 minutes Post-dose in UPDRS Part 3 Score** by Timepoint and Visit
(ITT Population)

Visit	Timepoint	Statistic	CVT-301 (N=xx)
TV2	Pre-dose	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
	10 mins Post-dose	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
		Change from Pre-dose	
		n	xx
		Mean	xx.x
		SD	xx.xx
		SEM	xx.x
		Median	xx.x
		Min, Max	xx, xx
		...	
	20 mins Post-dose		
	30 mins Post-dose		
	60 mins Post-dose		
Continue with TV3, TV4, TV5, TV6			

Note: TV = Treatment Visit;
Cross-reference: Listing 16.2.6.1.2

Table 14.2.3.1
Exploratory Efficacy Analysis: Subjects with a >=3 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit
(ITT Population)

Visit/Time Point	CVT-301 (N=xx) n (%)
TV2	
Any Time Post-dose	
n*	xx
Cumulative number of subjects having achieved the response	xx (xx.x)
10 mins Post-dose	
n*	xx
Number of subjects achieving the first response	xx (xx.x)
20 mins Post-dose	xx (xx.x)
n*	xx
Number of subjects achieving the first response	xx (xx.x)
Cumulative number of subjects having achieved the response[a]	xx (xx.x)
30 mins Post-dose	xx (xx.x)
n*	xx
Number of subjects achieving the first response	xx (xx.x)
Cumulative number of subjects having achieved the response	xx (xx.x)
60 mins Post-dose	xx (xx.x)
n*	xx
Number of subjects achieving the first response	xx (xx.x)
Cumulative number of subjects having achieved the response	xx (xx.x)
TV3 …	
TV4 …	
TV5 …	
TV6 …	

Note: TV = Treatment Visit; ; Percentages are based on n*, the number of subjects with UPDRS Part 3 performed at any time post-dose and pre-dose.
[a]Cumulative numbers of subjects refer to the subjects who achieved the first reduction before or at the time point.

Cross-reference: Listing 16.2.6.1.2

Table below will use the table 14.2.3.1 template except that percentages are based on N

Table 14.2.3.2
Additional Exploratory Efficacy Analysis: Subjects with a >=3 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit
With Percentages Based on N
(ITT Population)

Note: Percentages are based on the header count N.
Cross-reference: Listing 16.2.6.1.2

Table 14.2.3.3
Exploratory **Efficacy Analysis: Subjects with a >=6 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit**
(ITT Population)

Table 14.2.3.4
Exploratory **Efficacy Analysis: Subjects with a >=6 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit**
With Percentages Based on N
(ITT Population)

Note: TV = Treatment Visit; Percentages are based on the header count N.
Cross-reference: Listing 16.2.6.1.2

Table 14.2.3.5
Exploratory **Efficacy Analysis: Subjects with a >=11 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit**
(ITT Population)

Table 14.2.3.6
Exploratory **Efficacy Analysis: Subjects with a >=11 Reduction from Pre-dose to Post-dose in the UPDRS Part 3 Score by Visit**
With Percentages Based on N
(ITT Population)

Note: TV = Treatment Visit; Percentages are based on the header count N.
Cross-reference: Listing 16.2.6.1.2

Table 14.2.4.1
Exploratory Efficacy Analysis: Subjects Achieving Resolution of an OFF to an ON State within 60 Minutes by Visit
Worst Case Imputation [a]
(ITT Population)

Visit/ Category	Statistic	CVT-301 (N=xx)
TV2		
Turned ON within 60 Minutes		
Yes	n (%)	xx (xx.x)
No	n (%)	xx (xx.x)
Turned ON within 60 Minutes (Observed)		
Yes	n (%)	xx (xx.x)
No	n (%)	xx (xx.x)
Missing	n (%)	xx (xx.x)
TV3		
TV4		
TV5		
TV6		

Note: TV = Treatment Visit;
[a] The patient who achieved 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 will be counted as Yes. The missing values will be counted as non-resolved.
Cross-reference: Listing 16.2.6.2.1

Table 14.2.5.1.1
Exploratory Efficacy Analysis: Mean of Total Daily OFF Time by Visit
(ITT Population)

Visit	Statistic	O.C. (N=xx)	CVT-301 (N=xx)	p-value
Overall	Overall p-value			
	Baseline Hoehn and Yahr stage			0.xxx
	Screening Spirometry			0.xxx
	Treatment			0.xxx
	Visit			0.xxx
	Treatment-by-Visit Interaction			0.xxx
	Baseline Daily OFF time			0.xxx
TV2/OV2	n	xx	xx	
	LS Mean	xx.x	xx.x	
	SE (LS Mean)	xx.xx	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	(xx.x, xx.x)	
	LS Mean Difference (CVT-301 – O.C.)		xx.x	
	95% CI (LS Mean Difference)		(xx.x, xx.x)	
	p-value (LS Mean Difference)		0.xxx	
TV3/OV3				
...				

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the total daily OFF time at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. The total daily OFF time at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

Table below will use format Table 14.2.1.3.2 except for two treatment group.

Table 14.2.5.1.2
Sensitivity Analysis: Mean of Total Daily OFF Time by Visit
MI analysis with Missing At Random Assumption
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit;
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing at random. MMRM model uses the total daily OFF time at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. The total daily OFF time at baseline will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate at each visit.

Cross-reference: Listing 16.2.6.2.3.2

Table below will use the table 14.2.5.1.1 template except will be performed for "Hoehn & Yahr scale < 2.5 points" and "Hoehn & Yahr scale >= 2.5 points" and removed 'baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)' in the model. Footnote revised.

Table 14.2.5.1.3
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Baseline PD Severity
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the total daily OFF time at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. The total daily OFF time at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "Dyskinetic before TV1" and "Non-dyskinetic before TV1"

Table 14.2.5.1.4
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Baseline Dyskinesia
(ITT Population)

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "**Baseline Daily Levodopa Dose**<=Median of **Baseline Daily Levodopa Dose**" and "**Baseline Daily Levodopa Dose**>=Median of **Baseline Daily Levodopa Dose**".

Table 14.2.5.1.5
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Baseline Daily Levodopa Dose
(ITT Population)

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "PD Diary Mean Daily OFF Time during Screening < 4.5 Hours" and "PD Diary Mean Daily OFF Time during Screening >=4.5 Hours".

Table 14.2.5.1.6
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by PD Diary Mean Daily OFF Time during Screening
(ITT Population)

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "FEV1 <60% or FEV1/FVC ratio <70%" and "FEV1 ≥60% and FEV1/FVC ratio ≥70%"removed 'screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%' in the model. Footnote revised.

Table 14.2.5.1.7
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Screening Spirometry
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the total daily OFF time at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)) and the interaction between the treatment group and visit as fixed factors. The total daily OFF time at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "Non-elderly (<65 years)" and "Elderly (≥65 years) patients".

Table 14.2.5.1.8
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Age Group
(ITT Population)

Table below will use the table 14.2.5.1.1 template and footnote except will be performed for "Female" and "Male".

Table 14.2.5.1.9
Exploratory Efficacy Subgroup Analysis: Mean of Total Daily OFF Time by Visit by Gender
(ITT Population)

Table below will use the table 14.2.5.1.1 template.

Table 14.2.5.2
Exploratory Efficacy Analysis: Mean of Total Daily ON Time without Dyskinesia by Visit
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the **total daily ON time without dyskinesia** at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the **total daily ON time without dyskinesia** at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

Table 14.2.5.3
Exploratory Efficacy Analysis: Mean of Total Daily ON Time with non-Troublesome Dyskinesia by Visit
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the total daily ON time with non-troublesome dyskinesia at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the total daily ON time with non-troublesome dyskinesia at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

Table 14.2.5.4
Exploratory Efficacy Analysis: Mean of Total Daily ON Time with Troublesome Dyskinesia by Visit
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; MMRM model uses the total daily ON time with troublesome dyskinesia at each post-baseline visit (TV2, TV3,TV4, TV5 or TV6) as the dependent variable, and includes visit (TV2, TV3,TV4, TV5 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; the total daily ON time with troublesome dyskinesia at baseline will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.6.2.3.2

will have similar format as **Table 14.2.5.1.1**.

Table 14.2.6.1
Exploratory Efficacy Analysis: Subjects Global Impression of Change (PGI-C) by Visit
Worst Case Imputation [a]
(ITT Population)

Visit/Statistic	CVT-301 (N=xx) n (%)
TV4/OV4	
n	xx
Much Improved	xx (xx.x)
Improved	xx (xx.x)
A little Improved	xx (xx.x)
No Change	xx (xx.x)
A Little Worse	xx (xx.x)
Worse	xx (xx.x)
Much Worse	xx (xx.x)
Improved [b]	
Yes	xx (xx.x)
No	xx (xx.x)
Improved (Observed)	
Yes	xx (xx.x)
No	xx (xx.x)
Missing	xx (xx.x)
TV6/OV6	

Note: TV = Treatment Visit; OV = Observational Visit; Percentages are based on n, the number of subjects with PGI-C performed at each visit.
[a] The missing values will be counted as No.
[b] The patient who had PGI-C response of much improved, improved or a little improved will be counted as Yes.

Cross-reference: Listing 16.2.6.2.4

Table 14.2.7.1
Exploratory Efficacy Analysis: UPDRS Part 2 Score at TV4/OV4
(ITT Population)

Visit	Statistic	O. C. (N=xx)	CVT-301 (N=xx)
Baseline	Actual Value		
	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
TV4/OV4	Actual value		
	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	Change from Baseline		
	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	LS Mean	xx.xx	xx.xx
	SE (LS Mean)	xx.xxx	xx.xxx
	95% CI (LS Mean)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
	LS Mean Difference (CVT-301 - O. C.)		xx.xx
	95% CI (LS Mean Difference)		(xx.xx, xx.xx)
	p-value (LS Mean Difference)		0.xxx

Note: TV = Treatment Visit; OV = Observational Visit; Baseline is defined as the assessments performed at TV1/OV1. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline. An ANCOVA model with the treatment group and stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5) and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors and the baseline value as a covariate will be used to estimate the treatment differences.

Cross-reference: Listing 16.2.6.3.1

Table below s will use the table 14.2.7.1 template.

Table 14.2.7.2
Exploratory Efficacy Analysis: UPDRS Part 2 Score at TV6/OV6
(ITT Population)

Table below s will use the table 14.2.7.1 template with revised cross-reference

Table 14.2.8.1
Exploratory Efficacy Analysis: Schwab and England (S&E) Activities of Daily Living (ADL) Score at TV4/OV4
(ITT Population)

Table 14.2.8.2
Exploratory Efficacy Analysis: Schwab and England (S&E) Activities of Daily Living (ADL) Score at TV6/OV6
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; Baseline is defined as the assessments performed at TV1/OV1. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline. An ANCOVA model with the treatment group and stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors and the baseline value as a covariate will be used to estimate the treatment differences.

Cross-reference: Listing 16.2.6.3.2

Table below s will use the table 14.2.7.1 template with revised cross-reference

Table 14.2.9.1
Exploratory Efficacy Analysis: 39 Item Parkinson's disease Questionnaire (PDQ-39) Sub-scores and Summary Index Score at TV4/OV4
(ITT Population)

Table 14.2.9.2
Exploratory Efficacy Analysis: 39 Item Parkinson's disease Questionnaire (PDQ-39) Sub-scores and Summary Index Score at TV6/OV6
(ITT Population)

Note: TV = Treatment Visit; OV = Observational Visit; Baseline is defined as the assessments performed at TV1/OV1. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline. An ANCOVA model with the treatment group and stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors and the baseline value as a covariate will be used to estimate the treatment differences.

Cross-reference: Listing 16.2.6.3.2

Table 14.3.1.1
Extent of Exposure: Overall for CVT-301 Group Only
(Safety Population)

		002/003 (N=xx)	Naive (N=xx)	Total (N=xx)
Subjects with Dose Change	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Increase	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Decrease	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration of Exposure (days) [a]	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
	Summed Total	xxx	xxx	xxx
Total Number of Capsules Taken (Overall)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
TV1-<TV2	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
TV2-<TV3				
TV3-<TV4				
TV4-<TV5	...			
TV5-TV6	...			
Total Number of Doses Taken (Overall)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
TV1-<TV2	...			
TV2-<TV3	...			
TV3-<TV4	...			
TV4-<TV5				
TV5-TV6				
Average Daily Doses (Overall)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
TV1-<TV2	...			
TV2-<TV3	...			
TV3-<TV4	...			
TV4-<TV5				
TV5-TV6				
Average Daily Number of Capsules (Overall)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
TV1-<TV2				

TV2-<TV3
TV3-<TV4
TV4-<TV5
TV5-TV6

Note: TV = Treatment Visit; Total column is for all CVT-301 treated patients, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Data presented is self-reported by study participants and is subject to limitations of self-report measures.
[a] Duration of exposure (days) is calculated as documented last dose date-first dose date +1.
Cross-reference: Listing 16.2.5.1.3, 16.2.5.1.4, 16.2.5.1.5

Table 14.3.1.1
Extent of Exposure: Overall for CVT-301 Group Only
(Safety Population)

		002/003 (N=xx)	Naive (N=xx)	Total (N=xx)
Proportion of Days with >5 Doses per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 5 Doses per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 4 Doses per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 3 Doses per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 2 Doses per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 1 Dose per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Days with 0 Dose per Day	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using >5 Doses/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using 5 Doses/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using 4 Doses/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using 3 Doses/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using 2 Doses/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	...			
Proportion of Patients using 1 Dose/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
Proportion of Patients using 0 Dose/day at least once	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x

Note: TV = Treatment Visit; Total column is for all CVT-301 treated patients, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Data presented is self-reported by study participants and is subject to limitations of self-report measures.
[b] Duration of exposure (days) is calculated as documented last dose date-first dose date +1.
Cross-reference: Listing 16.2.5.1.1, 16.2.5.1.3

Table 14.3.1.2
In-Clinic Study Drug Administration
(Safety Population)

Visit	Parameter	Statistic	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)
TV1	Standard Morning Dose of LD-containing Medications to in-clinic OFF (mins)	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	<= 180 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 180 to <= 210 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 210 to <= 240 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 240 to <= 270 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 270 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	In-clinic OFF to Start of Study Drug Inhalation (mins)	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		...			
	<= 10 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 10 to <= 15 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 15 to <= 20 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 20 to <= 25 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 25 to <= 30 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	> 30 mins	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Standard Morning Dose of LD-containing Medications to Start of Study Drug Inhalation (mins)	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
	Duration of Study Drug Inhalation (mins)	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		...			
TV2	...				
TV3	...				
...					

Note: TV = Treatment Visit; Total column is for all CVT-301 treated patients, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on the number of subjects with results for each parameter at each treatment visit within each treatment group or Overall.

Cross-reference: Listing 16.2.5.1.2

Table 14.3.1.3
Distribution of Time of Study Drug Administration for CVT-301 Group Only
(Safety Population)

Time Interval	Statistic	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)
Total Study Medication Intakes	n	xx	xx	xx
00:00 -< 00:30	n (%)	xx (%)	xx (%)	xx (%)
00:30 -< 01:00	n (%)	xx (%)	xx (%)	xx (%)
01:00 -< 01:30	n (%)	xx (%)	xx (%)	xx (%)
01:30 -< 02:00	n (%)	xx (%)	xx (%)	xx (%)
...				
Continue with 30 mins interval until 23:30 -< 24:00				

Note: Total column is for all CVT-301 treated patients, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The percentage is based on the total # of study medication intakes.
Cross-reference: Listing 16.2.5.1.1

Table 14.3.2.1
Treatment-Emergent Adverse Events -Overall Summary
(Safety Population)

	O. C. (N=xx)		CVT- 301 002/003 (N=xx)		CVT- 301 Naive (N=xx)		CVT- 301 Total (N=xx)		Overall (N=xx)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Drug-related TEAEs [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Serious TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TEAEs Leading to Study Drug Interruption	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TEAEs Leading to Study Drug Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TEAEs Leading to Dose Reduction	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TEAEs Leading to Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-emergent adverse events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug.
[a] Adverse events are considered drug-related if the event is classified as possibly, probably, or definitely related to study drug.

Cross-reference: Listing 16.2.7.1

Table 14.3.2.2.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

		CVT- 301			
	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
System Organ Class Preferred Term [a]	Subjects Events n (%) n	Subjects Events n (%) n	Subjects Events n (%) n	Subjects Events n (%) n	Subjects Events n (%) n
Any TEAEs	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
System Organ Class	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
System Organ Class	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1

Programming note: The table will be sorted by total descending frequency of SOC and then, within a SOC, by total descending frequency of PT.

Table 14.3.2.2.2
Treatment-Emergent Adverse Events by Preferred Term
(Safety Population)

		CVT- 301			
	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
	Subjects Events	Subjects Events	Subjects Events	Subjects Events	Subjects Events
Preferred Term [a]	n (%) n	n (%) n	n (%) n	n (%) n	n (%) n
Any TEAEs	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term 4	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1

Programming note: The table will be sorted by total descending frequency of PT.

Table 14.3.2.3
Drug-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity
(Safety Population)

			CVT- 301			
System Organ Class Preferred Term [a]	Severity	O. C. (N=xx) n (%)	002/003 (N=xx) n (%)	Naive (N=xx) n (%)	Total (N=xx) n (%)	Overall (N=xx) n (%)
All TEAEs	Total	xx	xx	xx	xx	xx
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class	Total	xx	xx	xx	xx	xx
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	...					
Preferred Term						
...						
System Organ Class						
Preferred Term						
Preferred Term						
...						

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug. Adverse events are considered drug-related if the event is classified as possibly, probably, or definitely related to study drug. The percentages are calculated based on the total number of TEAEs.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1

Programming note: The table will be sorted by total descending frequency of SOC then PT in total row, total column.

Table 14.3.2.4
Drug -Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship
(Safety Population)

System Organ Class Preferred Term [a]	Maximal Severity [b]	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
All TEAEs	Total	xx	xx	xx	xx	xx
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probably Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definitely Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class	Total	xx	xx	xx	xx	xx
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probably Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definitely Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	...					
Preferred Term						
...						
System Organ Class						
Preferred Term						
Preferred Term						
...						

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug. Adverse events are considered drug-related if the event is classified as possibly, probably, or definitely related to study drug. The percentages are calculated based on the total number of TEAEs.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1

Programming note: The table will be sorted by Definitely Not Related descending frequency of SOC then PT in total row, total column.

Table below s will have same format as T14.3.2.4.1 and note:

Table below s will have same format as 14.3.2.2.1and note:

Table 14.3.2.5
Drug-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug Adverse events are considered drug-related if the event is classified as possibly, probably, or definitely related to study drug.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1

Table 14.3.2.6
Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1, Table 14.3.2.7

Table 14.3.2.7
Listing of Serious Adverse Events

Treatment Group: O. C.

Treatment Group: O. C. Subject ID	System Organ Class/ Preferred Term/ Verbatim Term [a]	AE Start Date and Time/ Study Day [b]	AE Stop Date and Time	I: Intensity R: Relationship to Study Medication A: Action Taken	Outcome	SAE? If Yes, Specify [c]
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/	ddmonyyyy	R: xxxxxxxx		
xxxx-xxx	xxxxxxxxx	-xx	Hh:mm	A: xxxxxxxxx	Resolved	Yes: 1
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/		R: xxxxxxxx		
	xxxxxxxxx	xx#	Ongoing	A: xxxxxxxxx	Unknown	No
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/	ddmonyyyy	R: xxxxxxxx		
xxxx-xxx	xxxxxxxxx	-xx	Hh:mm	A: xxxxxxxxx	Resolved	Yes: 2
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. TEAE=Treatment-emergent AE. SAE=Serious AE.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.
[b] TEAEs were flagged with a #. The AEs occurred on the clinic visit were flagged with *. Study day is relative to date of first study medication (date of first dose = Day 1).
[c] 1 = The event is fatal or life-threatening, 2 = The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns), 3 = The event results in unplanned in subject hospitalization or prolongation of existing hospitalization, 4 = The event is a congenital anomaly, 5 = The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

Cross-reference: Listing 16.2.7.1

Table below s will have same format as T14.3.2.7

Table 14.3.2.8
Listing of Adverse Events Leading to Death

Table below s will have same format as T14.3.2.2.1**and revised** Cross-reference

Table 14.3.2.9
Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Population)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Treatment-Emergent Adverse Events (TEAEs) are defined as all AEs that start after the patient receives the first dose of study drug Adverse events are considered drug-related if the event is classified as possibly, probably, or definitely related to study drug.
[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.

Cross-reference: Listing 16.2.7.1, table 14.3.2.10

Table below s will have same format as T14.3.2.7

Table 14.3.2.10
Listing of Severe Treatment-Emergent Adverse Events
(Safety Population)

Table below s will have same format as T14.3.2.2.1**and revised** Cross-reference

Table 14.3.2.11
Treatment-Emergent Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term
(Safety Population)

Cross-reference: Listing 16.2.7.1, table 14.3.2.12

Table below s will have same format as T14.3.2.7

Table 14.3.2.12
Listing of Adverse Events Leading to Study Drug Interruption

Table below s will have same format as T14.3.2.2.1**and revised** Cross-reference

Table 14.3.2.13
Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(Safety Population)

Cross-reference: Listing 16.2.7.1, table 14.3.2.14

Table below will have same format as T14.3.2.7

Table 14.3.2.14
Listing of Adverse Events Leading to Study Drug Discontinuation

Table below will have same format as T14.3.2.2.1**and revised** Cross-reference

Table 14.3.2.15
Treatment-Emergent Adverse Events Leading to Dose Reduction by System Organ Class and Preferred Term
(Safety Population)

Cross-reference: Listing 16.2.7.1, table 14.3.2.16

Table below will have same format as T14.3.2.7

Table 14.3.2.16
Listing of Adverse Events Leading to Dose Reduction

Table 14.3.2.17
Most Common Treatment-Emergent Adverse Events (Preferred Term Occurred in >10% of Over Patients) by System Organ Class and Preferred Term
(Safety Population)

Cross-reference: Listing 16.2.7.1, table 14.3.2.18

Table 14.3.2.18
Listing of Most Common Treatment-Emergent Adverse Events

Table 14.3.2.19
Time to first Onset of Most Common Treatment-Emergent Adverse Events (Preferred Term Occurred in >10% of Over Patients)
(Safety Population)

		CTV-301			
Parameter	O.C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
0 -< 30 Days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
30 -< 90 Days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
90 -< 180 Days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
180 -< 270 Days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 270 Days	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. TEAE=Treatment-emergent AE. Percentages are based on the number of subjects at each treatment group or Overall. Most common TEAEs is defined any AE preferred term occurred in greater than 10% of overall patients. Time to first onset of most common TEAE is calculated as onset of first common TEAE-first dose date (or date of OV1) +1).

Cross-reference: Listing 16.2.7.1

Table 14.3.4.1
Clinical Laboratory Results: PCS and PCSC Criteria

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 (1)	>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%

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; LLN = lower limit of normal range; NA = not applicable; PCS = potentially clinically significant; PCSC = potentially clinically significant changes; Baseline is defined as the assessments performed at TV1/OV1. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline. * fasting defined as >=4 hr from prior meal.

Table 14.3.4.1.1.1
Summary of Clinical Laboratory Results: Hematology
(Safety Population)

				CVT- 301			
Test (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
Test 1 (unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV3/OV3	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV4/OV4	…					
	…						
Test 2 (unit)	Baseline						
	...						
...							

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Baseline is defined as the TV1/OV1 assessment. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline.

Cross-reference: Listing 16.2.8.1.1

Programming Note: Sort by test alphabetically.

Table 14.3.4.1.1.2
Summary of Clinical Laboratory Results: Hematology Abnormal Values
(Safety Population)

Test (unit)	Visit Assessment	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Test 1 (unit)	SV1					
	n	xx	xx	xx	xx	xx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	SV2					
	n	xx	xx	xx	xx	xx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	...					
	TV3/OV3					
	...					
	Followup					
	...					
Test 2 (unit)						
...						

Note: SV = Screening Visit; TV = Treatment Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on n, the number of subjects with the test performed at each visit.
PCS = potentially clinically significant values. PCSC = potentially clinically significant changes.

Cross-reference: Listing 16.2.8.1.1, **Table 14.3.4.1.1.6**

Programming Note: Sort by tests alphabetically.

Table 14.3.4.1.1.3
Summary of Clinical Laboratory Results: Hematology Abnormal Values –Shift from Baseline
(Safety Population)

Test 1

		Baseline			
Treatment	Visit Assessment	Normal n (%)	Abnormal: Low n (%)	Abnormal: High n (%)	Total n (%)
O. C.	TV3/OV3				
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	…				
	Followup				
	...				
CVT-301 (002/003)					
CVT-301 (Naïve)					
CVT-301 Total					
Overall					
Continue with other tests					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on the number of subjects with the test performed at both baseline and the visit.

Cross-reference: Listing 16.2.8.1.1, **Table 14.3.4.1.1.6**

Programming Note: Sort by tests alphabetically.

Table 14.3.4.1.1.4
Summary of Clinical Laboratory Results: Hematology PCS Values –Shift from Baseline
(Safety Population)

Test 1

		Baseline			
Treatment	Visit Assessment	Not PCS n (%)	PCS: Low n (%)	PCS: High n (%)	Total n (%)
O. C.	TV3/OV3				
	Not PCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS: Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS: High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Followup				
	...				
CVT-301 (002/003)					
CVT-301 (Naïve)					
CVT-301 Total					
Overall					
Continue with other tests					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on the number of subjects with the test performed at both baseline and the visit.
PCS = potentially clinically significant values.

Cross-reference: Listing 16.2.8.1.1, **Table 14.3.4.1.1.6**

Programming Note: Sort by tests alphabetically.

Table 14.3.4.1.1.5
Summary of Clinical Laboratory Results: Hematology PCSC Values –Shift from Baseline
(Safety Population)

Test 1

Treatment	Visit Assessment	Normal (N=xx) n (%)	Abnormal: Low (N=xx) n (%)	Abnormal: High (N=xx) n (%)	Total (N=xx) n (%)
O. C.	TV4				
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal: High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total				
	Followup				
	...				
CVT-301 (002/003)					
CVT-301(Naïve)					
CVT-301 Total					
Overall					
Continue with other tests					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on the number of subjects with the test performed at both baseline and the visit.
PCSC = potentially clinically significant changes.

Cross-reference: Listing 16.2.8.1.1, **Table 14.3.4.1.1.6**

Programming Note: Sort by tests alphabetically.

Table 14.3.4.1.1.6
Clinical Laboratory Results – Hematology PCS and PCSC Values
(Safety Population)

Treatment Group: O. C.

Patient ID	Visit	Date and Time of Sample	Test Name (unit)	Normal Range	Result [a]
xxxx-xxx	Screening	ddmonyyyy hh:mm	xxxxxxx (xxx)	xxxx-xxx	Xx H**
			xxxxxxx (xxx)	xxxx-xxx	xx L*
			...		
	TV3	ddmonyyyy hh:mm	xxxxxxx (xxx)	xxxx-xxx	Xx L**
			xxxxxxx (xxx)	xxxx-xxx	xx H*
			...		
	OV3				
	Followup				
xxxx-xxx					
...					

Programmer note: Please display all values for the parameter if there is at least one PCS or PCSC for the parameter

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
L* = potentially clinically significant (PCS) low value, H* = PCS high value,
L** = potentially clinically significant change (PCSC) low, H** = PCSC high.

Cross-reference: Listing 16.2.8.1.1

Table below will have same format as T14.3.4.1.1.1

Table 14.3.4.1.2.1
Summary of Clinical Laboratory Results: Chemistry
(Safety Population)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Baseline is defined as the TV1/OV1 assessment. If the TV1/OV1 assessment is missing, the last non-missing screening assessment will be used as baseline.

Cross-reference: Listing 16.2.8.1.2

Table below will have same format as T14.3.4.1.1.2 with revised cross reference

Table 14.3.4.1.2.2
Summary of Clinical Laboratory Results: Chemistry Abnormal Values
(Safety Population)

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on n, the number of subjects with the test performed at each visit.

Cross-reference: Listing 16.2.8.1.2, **Table 14.3.4.1.2.6**

Table below will have same format as T14.3.4.1.1.3 with revised cross reference

Table 14.3.4.1.2.3
Summary of Clinical Laboratory Results: Chemistry Abnormal Values –Shift from Baseline
(Safety Population)

Cross-reference: Listing 16.2.8.1.2, Table 14.3.4.1.2.6

Table below will have same format as T14.3.4.1.1.4with revised cross reference

Table 14.3.4.1.2.4
Summary of Clinical Laboratory Results: Chemistry PCS Values –Shift from Baseline
(Safety Population)

Cross-reference: Listing 16.2.8.1.2, Table 14.3.4.1.2.6

Table below will have same format as T14.3.4.1.1.5with revised cross reference

Table 14.3.4.1.2.5
Summary of Clinical Laboratory Results: Chemistry PCSC Values –Shift from Baseline
(Safety Population)

Cross-reference: Listing 16.2.8.1.2, Table 14.3.4.1.2.6

Table below will have same format as T14.3.4.1.1.6 with revised cross reference

Table 14.3.4.1.2.6
Clinical Laboratory Results – Chemistry PCS and PCSC Values
(Safety Population)

Cross-reference: Listing 16.2.8.1.2

Table 14.3.4.2
Vital Signs: PCS and PCSC Criteria

Vital Sign Parameters (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	2x	0.5x
Respiration Rate (brpm)	>32	<8	1.5x	NA
SBP (Supine) (mmHg)	>200	<85	1.6x	0.2x
DBP (Supine) (mmHg)	>120	<40	1.2x	0.2x

Note: bpm = beats per minute; brpm = breaths per minute; NA = not applicable; SBP = Systolic Blood Pressure; DBP = Diastolic Blood pressure; PCS = potentially clinically significant; PCSC = potentially clinically significant change.
* Baseline values will be used for pre-dose and pre-dose values assessment at each treatment visits. Pre-dose values will be used for corresponding post-dose values assessment.

Table 14.3.4.2.1
Summary of Vital Signs: Actual Values and Change from Baseline across Visits
(Safety Population)

				CVT- 301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
Standard Systolic Blood Pressure (unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV2/OV2 Pre-dose	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV3/OV3 Pre-dose	...					
	…	...					
	Followup	...					
Standard Diastolic Blood Pressure (unit)							
...							

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The baseline is defined as the TV1/OV1 pre-dose value. If TV1/OV1 pre-dose value is missing, the last non-missing screening assessment will be used as baseline.

Cross-reference: Listing 16.2.8.2.1

Programming Note: Repeat for Standard Diastolic Blood Pressure, Standard Heart Rate, Standard Respiratory Rate, Upright Systolic Blood Pressure, Upright Diastolic Blood Pressure, Upright Heart Rate, Respiration Rate

Table 14.3.4.2.2
Summary of Vital Signs: Actual Values and Change from Pre-dose at dose at TV1
(Safety Population)

Parameter (unit)	Time Point	Statistic	CVT-301 (N=xx)
Standard Systolic Blood Pressure (unit)	Pre-dose	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min, Max	xx, xx
	10 mins Post-dose	Actual value	
		n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min, Max	xx, xx
		Change from Pre-dose	
		n	xx
		Mean	xx.x
		SD	xx.xx
		Median	xx.x
		Min, Max	xx, xx
	...		
Standard Diastolic Blood Pressure (unit)			
...			

Cross-reference: Listing 16.2.8.2.1

Programming Note: Repeat for Standard Diastolic Blood Pressure, Standard Heart Rate, Standard Respiratory Rate, Upright Systolic Blood Pressure, Upright Diastolic Blood Pressure, Upright Heart Rate, Respiration Rate

Table 14.3.4.2.3
Summary of Standard Vital Signs: PCS and PCSC Values by Visit
(Safety Population)

Parameter (unit)	Visit Assessment	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Standard Systolic Blood Pressure (unit)	SV1					
	n	xx	xx	xx	xx	xx
	PCS Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	SV2					
	n	xx	xx	xx	xx	xx
	PCS Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCS High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV1/OV1 Pre-dose					
	n	xx	xx	xx	xx	xx
	...					
	TV2/OV2 Pre-dose					
	...					
	TV3/OV3 Pre-dose					
	...					
	...					
	Followup					
	...					
Standard Diastolic Blood Pressure (unit)						
...						

Note: SV = Screening Visit; TV = Treatment Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on n, the number of subjects with the test performed at each visit.
PCS = potentially clinically significant values, PCSC = potentially clinically significant changes.

Cross-reference: Listing 16.2.8.2.1, Table 14.3.4.2.5

Programming Note: Repeat for Standard Diastolic Blood Pressure, Standard Heart Rate, Standard Respiratory Rate. Only visits with any PCS or PCSC values are included.

Table 14.3.4.2.4
Summary of Standard Vital Signs: PCS and PCSC Values by Scheduled Timepoint at TV1
(Safety Population)

Parameter (unit)	Timepoint Assessment	CVT- 301 (N=xx) n (%)
Standard Systolic Blood Pressure (unit)	Pre-dose	
	n	xx
	PCS Low	xx (xx.x)
	PCS High	xx (xx.x)
	PCSC Low	xx (xx.x)
	PCSC High	xx (xx.x)
	10 mins post-dose	
	n	xx
	PCS Low	xx (xx.x)
	PCS High	xx (xx.x)
	PCSC Low	xx (xx.x)
	PCSC High	xx (xx.x)
	20 mins post-dose	
	n	xx
	...	
	30 mins post-dose	
	...	
	60 mins post-dose	
	...	
Standard Diastolic Blood Pressure (unit)		
...		

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on n, the number of subjects with the test performed at each visit.
PCS = potentially clinically significant values, PCSC = potentially clinically significant changes.

Cross-reference: Listing 16.2.8.2.1, Table 14.3.4.2.5

Programming Note: Repeat for Standard Diastolic Blood Pressure, Standard Heart Rate, Standard Respiratory Rate. Only visits with any PCS or PCSC values are included.

Table 14.3.4.2.5
Standard Vital Signs: PCS and PCSC Values

Treatment Group: O. C.

Patient ID	Visit	Time Point	Date Performed	Time Performed	Position	Blood Pressure (mmHg) SBP	Blood Pressure (mmHg) DBP	Heart Rate (Beats/Min)	Respiratory Rate (Breaths/Min)
				hh:mm	SUPINE/SEMI-	xx			
xxxx-xxx	Screening		ddmonyyyy		SUPINE		xx	xx	xx
				hh:mm	STANDING	xx	Xx H	xx	xx
		Pre-dose		hh:mm	SUPINE/SEMI-	xx L**			
	TV3/OV3		ddmonyyyy		SUPINE		xx	xx	xx
				hh:mm	STANDING	xx L*	xx	xx	xx
		...							
	...								
xxxx-xxx									
CVT-301 (002/003)									
CVT-301(Naïve)									
CVT-301 Total									

Programmer note: Please display all related values if there is one Orthostatic Hypertension Data
...

Note: SV = Screening Visit; TV = Treatment Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. L* = potentially clinically significant (PCS) low value, H* = PCS high value,
L** = potentially clinically significant change (PCSC) low, H** = PCSC high.

Cross-reference: Listing 16.2.8.2.1

Table 14.3.4.2.6
Summary of Vital Signs: Orthostatic Hypotension by Visit
(Safety Population)

		CVT- 301			
Visit	O. C. (N=xx) n (%)	002/003 (N=xx) n (%)	Naive (N=xx) n (%)	Total (N=xx) n (%)	Overall (N=xx) n (%)
SV1					
n	xx	xx	xx	xx	xx
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SV2					
n	xx	xx	xx	xx	xx
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV1/OV1 Pre-dose					
n	xx	xx	xx	xx	xx
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2 Pre-dose					
...					
TV3/OV3 Pre-dose					
...					
…					
...					
Followup					
...					

Note: SV = Screening Visit; TV = Treatment Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on n, the number of subjects with the test performed at each visit.
Orthostatic hypotension is defined as a reduction in SBP of 20 mmHg or more, and/or a reduction in DBP of 10 mmHg or more, for the standing measurement compared to the semi-supine measurement.

Cross-reference: Listing 16.2.8.2.1 and Table 14.3.4.2.8

Table 14.3.4.2.7
Summary of Vital Signs: Orthostatic Hypotension by Scheduled Timepoint at TV1
(Safety Population)

Timepoint	CVT- 301 (N=xx) n (%)
Pre-dose	
n	xx
Yes	xx (xx.x)
No	xx (xx.x)
10 mins post-dose	
n	xx
Yes	xx (xx.x)
No	xx (xx.x)
20 mins post-dose	
n	xx
Yes	xx (xx.x)
No	xx (xx.x)
30 mins post-dose	
...	
60 mins post-dose	
...	

Percentages are based on n, the number of subjects with the test performed at each visit.
Orthostatic hypotension is defined as a reduction in SBP of 20 mmHg or more, and/or a reduction in DBP of 10 mmHg or more, for the standing measurement compared to the semi-supine measurement.

Cross-reference: Listing 16.2.8.2.1 and Table 14.3.4.2.8

Table 14.3.4.2.8
Orthostatic Vital Signs

Treatment Group: O. C.

Patient ID	Visit	Time Point	Date Performed	Time Performed	Position	Blood Pressure (mmHg) SBP	Blood Pressure (mmHg) DBP	Heart Rate (Beats/Min)	Respiratory Rate (Breaths/Min)
				hh:mm	SUPINE/SEMI-	xx			
xxxx-xxx	Screening		ddmonyyyy		SUPINE		xx	xx	xx
				hh:mm	STANDING *	xx	xx	xx	xx
		Pre-dose		hh:mm	SUPINE/SEMI-	xx			
	Visit 3		ddmonyyyy		SUPINE		xx	xx	xx
				hh:mm	STANDING *	xx	xx	xx	xx
		...							
	...								
xxxx-xxx									
CVT-301 (002/003)									
CVT-301(Naïve)									
CVT-301 Total									

Programmer note: Please display all related values if there is one Orthostatic Hypertension Data
...

Note: SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
* denotes orthostatic hypotension that is defined as a reduction in SBP of 20 mmHg or more, and/or a reduction in DBP of 10 mmHg or more, for the standing measurement compared to the Semi-supine measurement.
Cross-reference: Listing 16.2.8.2.1

Table 14.3.4.3
12-Lead ECG:PCS and PCSC Criteria

ECG Parameters(Units)	Criteria for PCS Values (Actual values)		Criteria for PCSC values (Change from Baseline or pre-dose values *)	
	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	NA
QTcF (msec)	>500	NA	>15% for baseline >=440 >30% for baseline <440	NA
Heart Rate (bpm)	>120	<35	NA	NA

Note: bpm = beats per minute; msec = Micro Second; NA = not applicable; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PCS = potentially clinically significant; PCSC = potentially clinically significant change.
* Baseline values will be used for pre-dose and pre-dose values assessment at each treatment visits. Pre-dose values will be used for corresponding post-dose values assessment.

Table 14.3.4.3.1
Summary of 12-Lead ECG: Actual Values and Change across Visits
(Safety Population)

				CVT- 301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
PR Interval (unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV1/OV1	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV3/OV3	...					
	...						
...							

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The baseline is defined as the TV1/OV1 pre-dose value. If TV1/OV1 pre-dose value is missing, the last non-missing screening assessment will be used as baseline.

Cross-reference: Listing 16.2.8.2.2

Programming Note: Repeat for other ECG parameters.

Table 14.3.4.3.2
Summary of 12-Lead ECG: PCS and PCSC Values
(Safety Population)

Parameter (unit)	Visit Assessment	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
PR Interval (unit)	TV1/OV1					
	n	xx	xx	xx	xx	xx
	PCS High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PCSC High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	...					
	TV3/OV3					
	...					

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on n, the number of subjects with the test performed at each visit.
PCS = potentially clinically significant values, PCSC = potentially clinically significant changes.

Cross-reference: Listing 16.2.8.2.2, Table 14.3.4.3.3

Programming Note: For PCS repeat for other applicable ECG parameters (QRS Interval, QTcB, QTcF, Heart Rate). For Heart Rate, both PCS Low and PCS High will be assessed.
For PCSC repeat for other applicable ECG parameters (QRS Interval, QTcB, QTcF). PCSC Low values will not be assessed.
Only visits with any PCS or PCSC values are included.

Table 14.3.4.3.3
12-Lead Electrocardiogram (ECG): PCS and PCSC Values

Treatment Group: O. C.

Patient ID	Visit	Time Point	Date and Time Of Assessment	Test (Unit)	Result
xxxx-xxx	SV1		ddmonyyyy hh:mm		
	OV3	Pre-dose	ddmonyyyy hh:mm	xxx (xxx)	xx H*
		+5mins			xx L**
		+20mins			
		+30mins			
		...			
	...				
xxxx-xxx					
...					
CVT-301 (002/003)					
CVT-301(Naïve)					
CVT-301 Total					

Programmer note: Please display all values for the parameter if there is at least one PCS or PCSC for the parameter

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Note: L* = potentially clinically significant (PCS) low value, H* = PCS high value,
L** = potentially clinically significant change (PCSC) low, H** = PCSC high.

Cross-reference: Listing 16.2.8.2.2

Table 14.3.4.4
Physical Examination
(Safety Population)

Visit	Assessment	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Screening	Any Clinically Significant Abnormal Findings					
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV1/OV1	Any Clinically Significant Abnormal Findings That Are New or Have Worsened					
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2						
TV3/OV3						
…						

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Cross-reference: Listing 16.2.8.2.3

Table 14.3.4.5.1.1
Summary of Spirometry (Neurology Office): Actual Values and Change from Baseline for FEV1 and FVC by Visit
(Safety Population)

				CVT- 301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
FEV1 (unit)	Screening (ON state)	Actual value					
	Screening (OFF state)	Actual value					
	TV1/OV1 Arrival	Actual value					
	Baseline	Actual value					
	TV2/OV2 Arrival	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline	...				
		Percent Change from Baseline (%)					
	TV3/OV3 Arrival	...					
	TV4/OV4 Arrival	...					
	TV5/OV5 Arrival						
	TV6/OV6 Arrival						
	…	...					
FVC, Percentage Predicted FEV1, Percentage Predicted FVC							

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Screening is the latest assessment during screening period. Baseline is defined as the TV1/OV1 arrival value. If the TV1/OV1 arrival value is missing, the last available value in ON state before the first dose of study drug is used.

Cross-reference: Listing 16.2.8.2.4.1

Programming Note: Repeat for Percentage predicted FEV1, *FVC, Percentage predicted FVC. No need to summarize percent change for Predicted* FEV1 and *Predicted FVC.*

Table 14.3.4.5.1.2
Summary of Spirometry (Neurology Office): Actual Values and Change from Baseline for FEV1 and FVC by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Table 14.3.4.5.1.3
Summary of Spirometry (Neurology Office): Actual Values and Change from Baseline for FEV1 and FVC by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Screening is the latest assessment during screening period. Baseline is defined as the TV1/OV1 arrival value. If the TV1/OV1 arrival value is missing, the last available value in ON state before the first dose of study drug is used. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.

Cross-reference: Listing 16.2.8.2.4.1

Programming Note: Repeat for Percentage predicted FEV1, *FVC, Percentage predicted FVC. No need to summarize percent change for Predicted* FEV1 and *Predicted FVC.*

Table 14.3.4.5.1.4
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1 by Visit
(Safety Population)

Visit	Statistic	O. C. (N=xx)	CVT-301 (N=xx)	p-value
Overall	Overall p-value			
	Baseline Hoehn and Yahr stage			0.xxx
	Screening Spirometry			0.xxx
	Treatment			0.xxx
	Visit			0.xxx
	Treatment-by-Visit Interaction			0.xxx
	Baseline Spirometry			0.xxx
TV2/OV2	n	xx	xx	
	LS Mean	xx.x	xx.x	
	SE (LS Mean)	xx.xx	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	(xx.x, xx.x)	
	LS Mean Difference (CVT-301 – O. C.)		xx.x	
	95% CI (LS Mean Difference)		(xx.x, xx.x)	
	p-value (LS Mean Difference)		0.xxx	
TV3/OV3				
TV4/OV4				
TV5/OV5				
TV6/OV6				

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the Change from baseline for FEV1 at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline FEV1 will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.5
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1 by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Table 14.3.4.5.1.6
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1 by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
MMRM model uses the Change from baseline for FEV1 at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline FEV1 will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.7
Sensitivity Analysis Using MMRM: Change from Baseline for FEV1 by Visit
MI analysis with Missing At Random Assumption
(Safety Population)

Visit/Statistic	O. C. (N=xx)	CVT-301 (N=xx)
TV2/OV2		
MI mean (SE)	xx.xx(x.xxx)	xx.xx(x.xxx)
MI Treatment Difference in Mean Change from Baseline (SE)		xx.xx(x.xxx)
95% CI (MI Treatment Difference)		(xx.xx, xx.xx)
P-Value		0.xxx
TV3/OV3		
TV4/OV4		
TV5/OV5		
TV6/OV6		

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing At Random. MMRM model uses the **Change from baseline for FEV1** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline FEV1 will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate of the treatment difference at each visit.

Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.8
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FEV1 by Visit
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the Change from baseline for percentage predicted FEV1 at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline Percentage predicted FEV1 will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.9
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FEV1 by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the Change from baseline for percentage predicted FEV1 at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline Percentage predicted FEV1 will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.10
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FEV1 by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
MMRM model uses the Change from baseline for percentage predicted FEV1 at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline Percentage predicted FEV1 will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.11
Sensitivity Analysis Using MMRM: Change from Baseline for Percentage Predicted FEV1 by Visit
MI analysis with Missing At Random Assumption
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing At Random. MMRM model uses the **change from baseline for percentage predicted FEV1** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline **percentage predicted FEV1** will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate of the treatment difference at each visit.

Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.12
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FVC by Visit
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the **Change from Baseline for FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.13
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FVC by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the **Change from Baseline for FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.14
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FVC by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
MMRM model uses the **Change from Baseline for FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.15
Sensitivity Analysis Using MMRM: Change from Baseline for FVC by Visit
MI analysis with Missing At Random Assumption
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing At Random. MMRM model uses the **change from baseline for FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline FVC will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate of the treatment difference at each visit.
Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.1.16
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FVC by Visit
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the change from baseline for percentage predicted FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline percentage predicted FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1
Will use format for 14.3.4.5.1.2

Table 14.3.4.5.1.17
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FVC by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the change from baseline for percentage predicted FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70%

versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline percentage predicted FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1
Will use format for 14.3.4.5.1.2

Table 14.3.4.5.1.18
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for Percentage Predicted FVC by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
MMRM model uses the change from baseline for percentage predicted FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline percentage predicted FVC will be included as a covariate, assuming an unstructured covariance matrix.
Cross-reference: Listing 16.2.8.2.4.1
Will use format for 14.3.4.5.1.2

Table 14.3.4.5.1.19
Sensitivity Analysis Using MMRM: Change from Baseline for Percentage Predicted FVC by Visit
MI analysis with Missing At Random Assumption
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing At Random. MMRM model uses the c**hange from Baseline for percentage predicted FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline **percentage predicted FVC** will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate of the treatment difference at each visit.

Cross-reference: Listing 16.2.8.2.4.1
Will use format for Table 14.3.4.5.1.2 and Table 14.3.4.5.1.3 respectively.

Table 14.3.4.5.2.1
Summary of Spirometry :(Neurology Office): Actual Values and Change from Baseline for FEV1/FVC by Visit
(Safety Population)

			CVT- 301			
Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
Screening (ON state)	Actual value					
	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Screening (OFF state)	...					
TV1/OV1 Arrival						
Baseline						
TV2/OV2 Arrival	Actual value					
	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Change from Baseline	...				
	Percent Change from Baseline					
TV3/OV3 Arrival						
TV4/OV4 Arrival						
TV5/OV5 Arrival						
TV6/OV6 Arrival						

SV = Screening Visit; TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Screening is the latest assessment during screening period. Baseline is defined as the TV1/OV1 arrival value. If the TV1/OV1 arrival value is missing, the last available value in ON state before the first dose of study drug is used.

Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.2.2
Summary of Spirometry :(Neurology Office): Actual Values and Change from Baseline for FEV1/FVC by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Table 14.3.4.5.2.3
Summary of Spirometry :(Neurology Office): Actual Values and Change from Baseline for FEV1/FVC by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Table 14.3.4.5.2.4
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1/FVC by Visit
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the change from baseline for FEV1/FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FEV1/FVC will be included as a covariate, assuming an unstructured covariance matrix.

Will use format for table 14.3.4.5.1.2

Table 14.3.4.5.2.5
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1/FVC by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort.
MMRM model uses the change from baseline for FEV1/FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FEV1/FVC will be included as a covariate, assuming an unstructured covariance matrix.

Will use format for table 14.3.4.5.1.2

Table 14.3.4.5.2.6
MMRM Analysis of Spirometry Data (Neurology Office): Change from Baseline for FEV1/FVC by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
MMRM model uses the change from baseline for FEV1/FVC at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors; Baseline FEV1/FVC will be included as a covariate, assuming an unstructured covariance matrix.

Will use format for table 14.3.4.5.1.2

Table 14.3.4.5.2.7
Sensitivity Analysis Using MMRM: Change from Baseline for FEV1/FVC by Visit
MI analysis with Missing At Random Assumption
(Safety Population)

Note: TV = Treatment Visit; OV = Observational Visit
The non-monotone 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 monotone missing values are imputed using pattern mixture model assuming missing At Random. MMRM model uses the change from baseline for **FEV1/FVC** at each post-baseline visit (TV2, TV3, TV4, TV5, TV6) as the dependent variable, and includes the treatment group (CVT-301 or O.C.), visit (TV2, TV3, TV4, TV5, TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) and the interaction between the treatment group and visit as fixed factors. Baseline FEV1/FVC will be included as a covariate, assuming an unstructured covariance matrix. The MIANALYZE procedure in SAS will be applied to combine the results from these datasets to derive an overall estimate of the treatment difference at each visit.

Cross-reference: Listing 16.2.8.2.4.1

Will use format for table 14.3.4.5.1.3

Table 14.3.4.5.3.1
Summary of Spirometry (Neurology Office): Summary of FEV1/FVC < 60% and <70% by Visit
(Safety Population)

			CVT- 301			
Category/Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
FEV1/FVC < 60%						
Screening (ON state)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screening (OFF state)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV1/OV1 Arrival	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2 Arrival	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...						
FEV1/FVC < 70%						
Screening (ON state)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screening (OFF state)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV1/OV1 Arrival	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2 Arrival	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…						
...						

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Screening is the latest assessment during screening period. Baseline is defined as the TV1/OV1 arrival value. If the TV1/OV1 arrival value is missing, the last available value in ON state before the first dose of study drug is used.

Cross-reference: Listing 16.2.8.2.4.1, **Table 14.3.4.5.8**

Table 14.3.4.5.3.2
Summary of Spirometry (Neurology Office): Summary of FEV1/FVC < 60% and <70% by Visit
Using Subset of Assessments Meeting the ATS Quality Criteria
(Safety Population)

Table 14.3.4.5.3.3
Summary of Spirometry (Neurology Office): Summary of FEV1/FVC < 60% and <70% by Visit
Excluding Patients with Co-efficient of Variation (CV) of FEV1 >7.5%
(Safety Population)

Note: SV = Screening Visit; TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Screening is the latest assessment during screening period. Baseline is defined as the TV1/OV1 arrival value. If the TV1/OV1 arrival value is missing, the last available value in ON state before the first dose of study drug is used. The CV will be calculated for each patient as standard deviation divided by the mean. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.
Cross-reference: Listing 16.2.8.2.4.1, **Table 14.3.4.5.8**

Table 14.3.4.5.4
Spirometry (Neurology Office): 70% or Smaller FEV1/FVC Values

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Time Point	Motor State	Date and Time of Assessment	Test (Unit)	Result
xxxx-xxx@	TV2	Pre-dose	ON	ddmonyyyy hh:mm	xxx (xxx)	Xx*
	TV3	Pre-dose	ON	ddmonyyyy hh:mm #	xxx (xxx)	Xx $
	...					

xxxx-xxx
Programmer note: please display all FEV1, FVC and FEV1/FVC from all timepoint if any criteria meet.

Continue with CVT-301 (Naïve)

Note: TV = Treatment Visit;
# indicates spirometry measurement not meeting ATS quality criteria. * indicates imputed values. $ indicates manual data @ indicates patients with Co-efficient of Variation (CV) of FEV1 >7.5%
Data with 70% or smaller FEV1/FVC Values at each timepoint/visit are included.

Cross-reference: Listing 16.2.8.2.4.1

Table 14.3.4.5.5
Summary of Spirometry (Neurology Office): Measurements Meeting ATS Quality Criteria
(Safety Population)

State	Statistic	O. C. (N=xx)	CVT- 301 002/003 (N=xx)	CVT- 301 Naive (N=xx)	CVT- 301 Total (N=xx)	Overall (N=xx)
Overall						
Total Number of Spirometry Measurements	n	xx	xxx	xxx	xxx	xx
Total Number (Percent) of Measurements Meeting ATS Quality Criteria [a]	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Number (Percent) of Measurements Not Meeting ATS Quality Criteria [a]	n (%)	xx (xx.x)	xx (xx.x	xx (xx.x	xx (xx.x	xx (xx.x
Reason for Not Meeting ATS Quality Criteria [b]						
Acceptable Effort of ANY and Repeatable Effort of 0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acceptable Effort of 3 and Repeatable Effort of 0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acceptable Effort of 2 and Repeatable Effort of 0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acceptable Effort of 1 and Repeatable Effort of 0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acceptable Effort of 0 and Repeatable Effort of 0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acceptable Effort of 2 and Repeatable Effort of 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Proportion of Measurements Meeting ATS Quality Criteria at Subject Level[c]	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
ON State						
...						
OFF State						
...						

Note: O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] Percent is based on the total number of spirometry measurements.
[b] Percent is based on the total number of spirometry measurements not meeting ATS quality criteria.
[c] For each subject, the proportion is calculated as spirometry measurements meeting ATS criteria divided by total the count of records with unique assessment date/time and non-missing ATS Quality Criteria Flag.
Cross-reference: Listing 16.2.8.2.4.1, Listing 16.2.8.2.4.3

Table 14.3.4.5.6
Summary of Spirometry (Pulmonary Function Facility): Actual Values and Change from Baseline for Calculated DLco Parameters by Visit
(Safety Population)

				CVT-301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
DLco predicted (unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV2/OV2	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline	...				
		Percent Change from Baseline (%)					
	TV4/OV4	...					
	TV5/OV5						
	TV6/OV6						
	…						

Continue with all Applicable Calculated Parameters

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The baseline is defined as the DLco results taken after SV2 and before randomization.

Cross-reference: **Listing 16.2.8.2.4.4**

Table 14.3.4.5.7
Summary of Spirometry (Pulmonary Function Facility): Actual Values and Change from Baseline for FEV1 and FVC by Visit
(Safety Population)

				CVT- 301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
FEV1 (unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV2/OV2	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline	...				
		Percent Change from Baseline (%)					
	TV4/OV4	...					
	TV5/OV5						
	TV6/OV6						

Continue with all Applicable Parameters

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.

The baseline is defined as the DLco results taken after SV2 and before randomization.

Cross-reference: **Listing 16.2.8.2.4.4**

Table 14.3.4.5.8
Summary of Spirometry (Pulmonary Function Facility): Actual Values and Change from Baseline for FEV1/FVC by Visit
(Safety Population)

				CVT- 301			
Parameter (unit)	Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
FEV1/FVC(unit)	Baseline	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	TV2/OV2	Actual value					
		n	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
		Change from Baseline	...				
		Percent Change from Baseline (%)					
	TV4/OV4						
	TV5/OV5	...					
	TV6/OV6						

Note: TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The baseline is defined as the DLco results taken after SV2 and before randomization.

Cross-reference: **Listing 16.2.8.2.4.4**

Table 14.3.4.5.9
Summary of Spirometry (Pulmonary Function Facility): Summary of FEV1/FVC < 60% and <70% by Visit
(Safety Population)

			CVT- 301			
Category/Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
FEV1/FVC < 60%						
Baseline	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV4/OV4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV5/OV5	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV6/OV6	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...						
FEV1/FVC < 70%						
Baseline	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV2/OV2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV4/OV4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV5/OV5	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV6/OV6	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...						

Note: TV = Treatment Visit; OV = Observational Visit. O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. The baseline is defined as the DLco results taken after SV2 and before randomization.

Cross-reference: **Listing 16.2.8.2.4.4, Table 14.3.4.5.19**

Table 14.3.4.5.10
Spirometry (Pulmonary Function Facility):70% or Smaller FEV1/FVC Values by Visit

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Motor State	Date and Time of Assessment	Test (Unit)	Result	Change from Baseline
xxxx-xxx	TV2/OV2	Pre-dose	ON	ddmonyyyy hh:mm	xxx (xxx)	xx	
	TV3/OV3	Pre-dose	ON	ddmonyyyy hh:mm #	xxx (xxx)	Xx $	
	...						

xxxx-xxx
Programmer note: please display all FEV1, FVC and FEV1/FVC from all timepoint if any criteria meet.

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; OV = Observational Visit;
# indicates spirometry measurement not meeting ATS quality criteria. * indicates imputed values. $ indicates manual data.
Data with 70% or smaller FEV1/FVC Values are included.

Cross-reference: Listing 16.2.8.2.4.4

Table 14.3.4.5.11
Summary of Spirometry (Pulmonary Function Facility): Measurements Meeting ATS Quality Criteria
(Safety Population)

State	Statistic	O.C. (N=5)	CVT-301 002/003 (N=7)	CVT-301 Naive (N=8)	CVT-301 Total (N=20)	Overall (N=xx)
Overall						
Total Number of Spirometry/DLCO Measurements	n	xx	xx	xx	xx	
Total Number (Percent) of Spirometry Measurements Meeting ATS Quality Criteria [a]	n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Total Number (Percent) of Spirometry Measurements Not Meeting ATS Quality Criteria [b]	n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Total Number (Percent) of DLCO Measurements Meeting ATS Quality Criteria [a]	n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Total Number (Percent) of DLCO Measurements Not Meeting ATS Quality Criteria [b]	n (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Proportion of Spirometry Measurements Meeting ATS Quality Criteria at Subject Level[c]	n	xx	xx	xx	xx	xx
	Mean	0.xxxx	0.xxxx	0.xxxx	0.xxxx	0.xxxx
	SD	0.xxxxx	0.xxxxx	0.xxxxx	0.xxxxx	0.xxxxx
	Median	0.xxxx	0.xxxx	0.xxxx	0.xxxx	0.xxxx
	Min, Max	0.xxx, x.xxx	0.xxx, x.xxx	0.xxx, x.xxx	0.xxx, x.xxx	0.xxx, x.xxx
Proportion of DLCO Measurements Meeting ATS Quality Criteria at Subject Level[c]	n	xx	xx	xx	xx	
	Mean	0.xxxx	0.xxxx	0.xxxx	0.xxxx	
	…					

Note: TV = Treatment Visit; OV = Observational Visit; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] Percent is based on the total number of DLco measurements.
[b] Percent is based on the total number of DLco measurements not meeting ATS quality criteria.
[c] For each subject, the proportion is calculated as Dlco measurements meeting ATS criteria divided by total the count of records with unique assessment date/time and non-missing ATS Quality Criteria Flag.
Cross-reference: **Listing 16.2.8.2.4.4, Listing 16.2.8.2.4.6**

Table 14.3.4.6.1
Summary of Columbia-Suicide Severity Rating Scale (C-SSRS)
(Safety Population)

Section Item	Visit Assessment	O. C. (N=xx) n (%)	CVT- 301 002/003 (N=xx) n (%)	CVT- 301 Naive (N=xx) n (%)	CVT- 301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Baseline (TV1/OV1)						
Any Suicidal Ideation or Behavior		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Ideation		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Behavior		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Post Baseline						
Any Suicidal Ideation or Behavior		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Ideation		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Behavior		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Suicidal Ideation						
Wish to be Dead	TV1/OV1					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV2/OV2					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV3/OV3	...				
	TV4/OV4	...				
	TV5/OV5	...				
	TV6/OV6					
Non-Specific Active Suicidal Thoughts						
...						
Intensity of Ideation						
Suicidal Behavior						
TV2/OV2...						
...						

Note: TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on n, the number of subjects assessed at each visit.

Cross-reference: Listing 16.2.8.2.5

Table 14.3.4.6.2
Shift from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS)
(Safety Population)

		TV1/OV1 n (%)				
	Baseline	**No Suicidal Behavior or Ideation**	**Suicidal Ideation**	**Suicidal Behavior**	**Missing**	**Total**
O. C. (N=xx)	No Suicidal Ideation or Behavior	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
	Suicidal Ideation	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
	Suicidal Behavior	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
CVT-301 (002/003) (N=xx)	No Suicidal Ideation or Behavior	xxx (xx.x)	xxx (xx.x)	xxx (xx.%)	xx (xx.%)	xx (xx.x)
	Suicidal Ideation	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
	Suicidal Behavior	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)
	Missing	xx (xx.x)	xx (xx.x)	xx (xx.%)	xx (xx.%)	xx (xx.x)

Continue with CVT-301 (Naïve), CVT-301 Total and Overall

Continued with TV2/OV2 TV3/OV3, TV4/OV4, …

Note: O.C. rows is for the patients in Observational Cohort, 002/003 rows is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
Percentages are based on N, the number of subjects in each treatment group.

Cross-reference: Listing 16.2.8.2.5

Table 14.3.4.7
Summary of Epworth Sleepiness Scale Total Score: Actual Values and Change from Baseline by Visit
(Safety Population)

			CVT- 301			
Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
Baseline	Actual value					
	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
TV4/OV4	Actual value					
	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
	Change from Baseline					
	n	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
TV6/OV6	...					

Note: TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Baseline is the last non-missing assessment before the first dose of study drug.

Cross-reference: Listing 16.2.8.2.6

Table 14.3.4.8
Summary of Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (QUIP) by Visit
(Safety Population)

Section Item	Visit Assessment	O. C. (N=xx) n (%)	CVT-301 002/003 (N=xx) n (%)	CVT-301 Naive (N=xx) n (%)	CVT-301 Total (N=xx) n (%)	Overall (N=xx) n (%)
Any Impulse or Other Compulsive Behaviors	TV1/OV1					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV4/OV4					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	...					
	TV6/OV6					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Impulse Behaviors	TV1/OV1					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV4/OV4					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	...					
	TV6/OV6					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Other Compulsive Behaviors	TV1/OV1					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV4/OV4					

	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV6/OV6					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Impulse Control Disorders						
	TV1/OV1					
Compulsive Gambling	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	TV4/OV4					
	n	xx	xx	xx	xx	xx
	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	...					
Compulsive Sexual Behavior	...					
Compulsive Buying						
Compulsive Eating						
Other Compulsive Behaviors						
Hobbyism						
Punding						
Walkabout						
Compulsive Medication Use						

Note: TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Percentages are based on n, the number of subjects assessed at each visit.

Cross-reference: Listing 16.2.8.2.7

Table 14.3.4.9.1
MMRM Analysis of UPDRS Part 4: Change from Baseline in the UPDRS Part 4 Score by Visit
(Safety Population)

Visit	Statistic	CVT-301 (N=xx)	p-value
Overall	Overall p-value		
	Baseline Hoehn and Yahr stage		0.xxx
	Screening Spirometry		0.xxx
	Visit		0.xxx
	Baseline UPDRS Part 3 Score		0.xxx
TV4	n	xx	
	LS Mean	xx.x	
	SE (LS Mean)	xx.xx	
	95% CI (LS Mean)	(xx.x, xx.x)	
TV6			

Note: TV = Treatment Visit;
MMRM model uses the change from baseline in UPDRS Part 4 total scores at each post-baseline visit (TV4, TV6) as the dependent variable, and includes visit (TV4 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors;
The baseline UPDRS part 4 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.8.2.8.2

Tables below will have similar format as Table 14.3.4.9.1

Table 14.3.4.9.2
MMRM Analysis of UPDRS Part 4 D**yskinesias Score**: Change from Baseline in the UPDRS Part 4 Score by Visit
(Safety Population)

Note: TV = Treatment Visit;
MMRM model uses the change from baseline in UPDRS Part 4 **D**yskinesias scores at each post-baseline visit (TV4, TV6) as the dependent variable, and includes visit (TV4 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; The baseline UPDRS part 4 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.8.2.8.2

Table 14.3.4.9.3
MMRM Analysis of UPDRS Part 4 **Fluctuations Score**: Change from Baseline in the UPDRS Part 4 Score by Visit
(Safety Population)

Note: TV = Treatment Visit;
MMRM model uses the change from baseline in UPDRS Part 4 Fluctuations scores at each post-baseline visit (TV4, TV6) as the dependent variable, and includes visit (TV4 or TV6), the stratification variables (baseline Hoehn and Yahr stage (<2.5 versus ≥2.5)and screening spirometry ([FEV1] <60% or FEV1/forced vital capacity [FVC] ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%)) as fixed factors; The baseline UPDRS part 4 score will be included as a covariate, assuming an unstructured covariance matrix.

Cross-reference: Listing 16.2.8.2.8.2

Table 14.3.4.9.4
Summary of UPDRS Part 4: Actual Values and Change from Baseline by Visit
(Safety Population)

Visit	Statistic	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)
Baseline	Actual value			
	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
TV4/OV4	Actual value			
	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
	Change from Baseline			
	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
TV6/OV6				
...				

Note: TV = Treatment Visit; OV = Observational Cohort; Total column is for all CVT-301 treated patients, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients. Baseline is the last non-missing assessment before the first dose of study drug.

Cross-reference: Listing 16.2.8.2.6

Table below will have similar format as Table 14.3.4.9.4

Table 14.3.4.9.5
Summary of UPDRS Part 4 Dyskinesias Score: Actual Values and Change from Baseline by Visit
(Safety Population)

Table 14.3.4.9.6
Summary of UPDRS Part 4 Fluctuations Score: Actual Values and Change from Baseline by Visit
(Safety Population)

Table 14.3.4.10
Dyskinesia: Occurrence and Severity (In-clinic) by Visit
(ITT Population)

			CVT-301			
Visit	Statistic	O. C. (N=xx)	002/003 (N=xx)	Naive (N=xx)	Total (N=xx)	Overall (N=xx)
TV2/OV2	Dyskinesia					
	Yes (Percentages based on N)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No (Percentages based on N)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severity of Dyskinesia					
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TV3/OV3	...					

…

Note: TV = Treatment Visit; OV = Observational Cohort; O.C. column is for the patients in Observational Cohort, 002/003 column is for the patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and Naïve is for the CVT-301 naive patients.
[a] The data for which a subject was dyskinetic already before the study drug administration was excluded from summary.

Cross-reference: Listing 16.2.6.2.1

Attachment 2 Listing Mock-ups

Table of Contents

Listing 16.2.1
Patient Disposition

Treatment Group: Observational Cohort

Patient ID	Date of First Dose	Date of Last Dose	Date of Completion/ Withdrawal (Study Day) [a]	Completed Study?	Primary Reason for Withdrawal	Screen Failure/Date
xxxx-xxx	ddmonyyyy	ddmonyyyy	ddmonyyyy	Yes		
xxxx-xxx	ddmonyyyy	ddmonyyyy	ddmonyyyy	No	Adverse Event: AE #x	Yes
xxxx-xxx	ddmonyyyy	ddmonyyyy	ddmonyyyy	No	Lack of Efficacy	
xxxx-xxx	ddmonyyyy	ddmonyyyy	ddmonyyyy	No	Patient Withdrew Consent	No
xxxx-xxx	ddmonyyyy	ddmonyyyy	ddmonyyyy	No	Protocol Violation: xxxxxxxxxx	

...

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: [a] Study Day = Date of Completion/Withdrawal – Date of first Dose + 1.

Listing 16.2.2.1
Protocol Deviations

Treatment Group: Observational Cohort

Patient ID	Deviation Type	Deviation Description	Created Date	Major Deviation	Affect Pulmonary Assessments
xxxx-xxx	xxxxxxxxxxx	xxxxxxxxxxxxxxxxxx	ddmonyyyy		
		xxxxxxxxxxxxxxxxxx	ddmonyyyy		
xxxx-xxx	xxxxxxxxxxx	xxxxxxxxxxxxxxxxxx	ddmonyyyy	Yes	Yes
	xxxxxxxxxxx	xxxxxxxxxxxxxxxxxx	ddmonyyyy		

...
Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.3.1
Inclusion Criteria not Met at Screening

Inclusion Criteria:

1. Has signed and dated an IRB/IEC-approved informed consent form before any protocol-specific screening procedures are performed.
2. Is a male or female aged 30 to 80 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
3. Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the United Kingdom (UK) Brain Bank criteria, diagnosed after the age of 30 years.
4. Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
5. Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.
6. Patients must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/DDI-containing regimen, which must include doses at least 4 times during the waking day and a total daily LD dose of ≤1600 mg (exclusive of PRN LD-containing medications).
7. Patients should be stable on other PD medications for at least 4 weeks prior to SV1.
8. Patients must have a ≥25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.
9. Patients must understand (with or without caregiver assistance) their daily medication regimen and must agree that they will not change their daily medication doses during the study.
10. Patients must have normal cognition as confirmed by a score of ≥25 on the Mini Mental State Examination (MMSE).
11. Patients must be able to perform a spirometry maneuver in the ON and OFF states and must have a screening FEV1 ≥50% of predicted, and a FEV1/FVC ratio >60% of predicted in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patient with FEV1 <60% or FEV1/FVC <70% in order to determine eligibility. Patients with an FEV1/FVC <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.)

Listing **16.2.3.1**
Inclusion Criteria not Met at Screening

Treatment Group: Observational Cohort

Patient ID	Any Criterion Violation at SV1	Criterion Not Met at SV1		Patient Has >= 2 Hours of OFF Time during the Waking Day Confirmed by Diary.	Criterion Not Met at SV2	
		Criterion Number	Comment		Criterion Number	Comment
xxxx-xxx	Yes	x	xxxxxxx	x	x	xxxxxxx
		x	xxxxxxx	x	x	xxxxxxx
xxxx-xxx		x	xxxxxxx	x	x	xxxxxxx
xxxx-xxx						
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.3.2
Exclusion Criteria Met at Screening

Exclusion Criteria

1. Patients who have dyskinesia of a severity that would significantly interfere with their ability to participate or perform study procedures.
2. Pregnant or lactating females or females wishing to become pregnant.
3. Patients who have any known contraindication to the use of LD, including a history of malignant melanoma or a history of narrow-angle glaucoma.
4. Patients who have had previous surgery for PD (including but not limited to deep brain stimulation or cell transplantation) or plan to have stereotactic surgery during the study period.
5. Patients with a history of psychotic symptoms requiring treatment, or suicidal ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of anti-depressant medications and certain low-dose atypical antipsychotic medications are permitted).
6. Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.
7. Patients taking certain prohibited medications (see Section 9.4.2).
8. Patients with a history of drug or alcohol abuse within the prior 12 months.
9. Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years (or if a patient is receiving treatment for any of these conditions).
10. Patients with any contraindication to performing routine spirometry or who are unable to perform a spirometry maneuver (see Appendix 14 for a list of contraindications).
11. Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment.
12. Patients with any condition that in the investigator's opinion would make patients unable to comply with study procedures or make them unsuitable for participation in the study.
13. Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety. Potential issues of concern should be raised to the medical monitor during eligibility review.
14. Patients who have participated in any prior CVT-301 study, regardless of treatment group assignment.

Listing 16.2.3.2
Exclusion Criteria Met at Screening

Treatment Group: Observational Cohort

Patient ID	Any Criterion Violation at SV1	Criterion Met at SV1		Patient Has >= 2 Hours of OFF time during the Waking Day Confirmed by Diary.	Criterion Met at SV2	
		Criterion Number	Comment		Criterion Number	Comment
xxxx-xxx	Yes	x	xxxxxxx	x	x	xxxxxxx
		x	xxxxxxx	x	x	xxxxxxx
xxxx-xxx		x	xxxxxxx	x	x	xxxxxxx
xxxx-xxx						
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.3.3
Analysis Populations

Treatment Group: Observational Cohort

Patient ID	Safety Population	ITT Population	Completed Visit					
			TV1/OV1	TV2/OV2	TV3/OV3	TV4/OV4	TV5/OV5	TV6/OV6
xxxx-xxx	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
xxxx-xxx	No	No	Yes	Yes	Yes	Yes	Yes	Yes

...
Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.4.1
Demographics

Treatment Group: Observational Cohort

Patient ID	Date of Informed Consent	Date of Birth	Age (years) [a]	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2) [b]
xxxx-xxx	ddmonyyyy	ddmonyyyy	xx	Male	White	Hispanic or Latino	xxx.x	xx.x	xx.x
xxxx-xxx	ddmonyyyy	ddmonyyyy	xx	Male	Black or African American	Not Hispanic or Latino	xxx.x	xx.x	xx.x
xxxx-xxx	ddmonyyyy	ddmonyyyy	xx	Female	Other: xxxxx	Hispanic or Latino	xxx.x	xx.x	xx.x
xxxx-xxx	ddmonyyyy	ddmonyyyy	xx	Female	Asian	Unknown	xxx.x	xx.x	xx.x

...

Continue with CVT-301 (002/003), CVT-301 (Naïve)

[a] Age was calculated as the difference between date of birth and date of Informed Consent, in years.
[b] BMI was calculated as weight (kg) / [height (m)]^2.

Listing 16.2.4.2
Medical History

Treatment Group: Observational Cohort

Patient ID	Body System	Description	System Organ Class/ Preferred Term [a]	Start Date	Stop Date
xxxx-xxx	HEENT	xxxxxxxxxxxx	xxxxxxxxxxxxxx/ xxxxxxxxx	ddmonyyyy	ddmonyyyy
	Dermatological	xxxxxxxxxxxx	xxxxxxxxxxxxxx/ xxxxxxxxx	ddmonyyyy	Ongoing
	Psychiatric	xxxxxxxxxxxx	xxxxxxxxxxxxxx/ xxxxxxxxx	ddmonyyyy	Ongoing
	Neurological	xxxxxxxxxxxx	xxxxxxxxxxxxxx/ xxxxxxxxx	ddmonyyyy	Ongoing
	...			ddmonyyyy	Ongoing
	Other: xxxxxx			Unknown	Unknown
xxxx-xxx					
...					

Continue with CVT-301 (002/003), CVT-301 (Naïve)

[a] Medical history data were coded into system organ class and preferred term by using MedDRA version 17.0.

Listing 16.2.4.3
Parkinson's Disease History

Treatment Group: Observational Cohort

Patient ID	Date of Diagnosis	Start Date of Levodopa Treatment	Date of Onset of Motor Fluctuation (Wearing Off) Episodes
xxxx-xxx	monyyyy	monyyyy	monyyyy
xxxx-xxx	monyyyy	monyyyy	monyyyy
xxxx-xxx	monyyyy	monyyyy	monyyyy
xxxx-xxx	monyyyy	monyyyy	monyyyy

...

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.4.4
Smoking History

Treatment Group: Observational Cohort

Patient ID	Ever Smoked Cigarettes	Age Started	Current Smoker	Smoking Status	Age Quitted	If Former or Current Smoker, Average Number of Cigarettes per Day	If Former or Current Smoker, Number of Years Smoked
xxxx-xxx	Yes	25	No	Former	xx	xx	xx
xxxx-xxx	Yes	26	Yes	Current	xx	xx	xx
xxxx-xxx	No			Never			
xxxx-xxx							
...							

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Number of Years Smoked = (Age-Age Started+1)(Current Smoker) OR =(Age Quitted-Age Started+1)(Former Smoker).

Listing 16.2.4.5
ON and OFF Concordance Testing at Screening

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Has the Patient Been Tested for Competence in self-rating with at least 75% concordance with the ratings of the examiner?
xxxx-xxx	SV1	ddmonyyyy	Yes
	SV2	Not Done	
xxxx-xxx	UNS	ddmonyyyy	No
	SV1	ddmonyyyy	Yes
...			

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; UNS = Unscheduled;

Listing 16.2.4.6
Modified Hoehn and Yahr Staging in "ON" State at Screening

Treatment Group: Observational Cohort

Patient ID	Date of Assessment	Stage in "ON" State [a]
xxxx-xxx	ddmonyyyy	0 = No signs of disease
xxxx-xxx	ddmonyyyy	1 = Unilateral disease
xxxx-xxx	Not Done, xxxxxx	
...		

Continue with CVT-301 (002/003), CVT-301 (Naïve)

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

Listing 16.2.4.7
Mini Mental State Examination (MMSE) at Screening

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total Score [a]
xxxx-xxx	SV1	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	xx
xxxx-xxx	SV2	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	xx
xxxx-xxx		Not Done, xxxx												
...														
Continue with CVT-301 (002/003), CVT-301 (Naïve)														

Note: SV= Screening Visit; UNS=Unscheduled Visit;
[a] >=25 points = normal, 21-24 points = mild cognitive impairment, 10-20 points = moderate cognitive impairment, 0-9 points = severe cognitive impairment.

Listing 16.2.4.8
Parkinson's Disease Diary Data at Screening: Derived Time

Treatment Group: Observational Cohort

Patient ID	Mean OFF Time (hours)	Mean Daily ON Time Without Dyskinesia (hours)	Mean Daily ON Time With Non-troublesome Dyskinesia (hours)	Mean Daily ON Time With Troublesome Dyskinesia (hours)	Dyskinetic Before TV1 [a]
xxxx-xxx	xx.x	xx.x	xx.x	xx.x	Yes
xxxx-xxx	xx.x	xx.x	xx.x	xx.x	No
xxxx-xxx	xx.x	xx.x	xx.x	xx.x	
xxxx-xxx	xx.x	xx.x	xx.x	xx.x	
...					

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; All diary data were normalized to 16 awake hours per day.
[a] 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 are classified as dyskinetic.

Listing 16.2.4.9
Screening ON/OFF Log

Treatment Group: Observational Cohort

Patient ID	Date of Assessment	Time of Start of OFF Episode	Changed the Timing of Usual LD Medication?	Take an Extra Dose of LD/ Other Parkinson's Medication?	Daily Number of OFF Episodes Experienced
xxxx-xxx	ddmonyyyy	hh:mm a.m.	Yes	Yes	xx
		hh:mm a.m.	No	No	
	ddmonyyyy	hh:mm p.m.	No		
	...				
xxxx-xxx					
...					

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.4.10
Randomization

Treatment Group: Observational Cohort

Patient ID	Date of Randomization	Kit Number	Baseline Disease Severity [a]	Screening Spirometry	Country	Site
xxxx-xxx	ddmonyyyy	NA	Low	FEV1 <60% or FEV1/FVC ratio <70%	US	xx
xxxx-xxx	ddmonyyyy	NA	High	FEV1 ≥60% and FEV1/FVC ratio ≥70%	US	xx
xxxx-xxx	ddmonyyyy	NA	High	FEV1 ≥60% and FEV1/FVC ratio ≥70%	Canada	xx
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

[a] Low = Hoehn and Yahr Stage < 2.5, High = Hoehn and Yahr Stage >= 2.5.
[b] 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 Visit 3 are classified as dyskinetic.

Listing 16.2.4.11.1
Prior and Concomitant Medications

Treatment Group: Observational Cohort

Patient ID	ATC Level 1/ ATC Level 2 [a]	Preferred Term [a]/ Medication Name	Start/ Stop Date	P/C [b]	Dose (Unit)	Frequency	Route	Indication
	xxxxxxxx/	xxxxxxxx/					xxxxx	
xxxx-xxx	xxxxxxxxxxxx	xxxxxxxxxxxx	Ddmonyyyy/ddmonyyyy	P	xxxxx (xxx)	xxx		Medical History: x
		xxxxxxxx/	ddmonyyyy/					
	xxxxxxxx/	xxxxxxxxxxxx	ddmonyyyy				xxxxx	
	xxxxxxxxxxxx			C	xxxxx (xxx)	xxx		Adverse Event: x
		xxxxxxxx/					xxxxx	
		xxxxxxxxxxxx	ddmonyyyy/ Ongoing	C	xxxxx (xxx)	Other: xxx		...
xxxx-xxx								
...								
Continue with CVT-301 (002/003), CVT-301 (Naïve)								

[a] Medications were coded into ATC and preferred term using the WHO Drug Dictionary Q1March2014.
[b] P=Prior, C=Concomitant.

Listing 16.2.4.11.2
Parkinson's disease Treatment Medications at Baseline

Treatment Group: Observational Cohort

Patient ID	ATC Level 1/ ATC Level 2 [a]	Preferred Term [a]/ Medication Name	Start/ Stop Date	P/C [b]	Dose (Unit)	Frequency	Route	Indication
	xxxxxxxx/	xxxxxxxx/					xxxxx	
xxxx-xxx	xxxxxxxxxxxx	xxxxxxxxxxxx	ddmonyyyy/ddmonyyyy	P	xxxxx (xxx)	xxx		Medical History: x
	xxxxxxxx/	xxxxxxxx/					xxxxx	
	xxxxxxxxxxxx	xxxxxxxxxxxx	ddmonyyyy/ddmonyyyy	C	xxxxx (xxx)	xxx		Adverse Event: x
		xxxxxxxx/					xxxxx	
		xxxxxxxxxxxx	ddmonyyyy/ Ongoing	C	xxxxx (xxx)	Other: xxx		...
xxxx-xxx								
...								

Continue with CVT-301 (002/003), CVT-301 (Naïve)

[a] Medications were coded into ATC and preferred term using the WHO Drug Dictionary, Q1March2014. The medications which start with ATC code N04 are considered as baseline PD treatment medications.

Listing 16.2.4.12
Baseline Pulmonary Assessment Part 2 - **Pulmonary History**

Part 2: Pulmonary History
A. Asthma Questions:
1. Have you ever been told by an MD or other health care provider that you have asthma?/Details
2. If yes, how old were you when you were diagnosed with asthma?(years)
3. Do you still have asthma?
4. If no, at what age did your asthma resolve?
5. If yes, do you take medicine for asthma?
6. Which medicine(s) do you take for asthma?
7. What things cause your asthma to worsen or asthma attacks to occur?

B. COPD Questions:
1. Have you ever been told by an MD or other health care provider that you have smoker's cough, COPD, emphysema, or chronic bronchitis?
2. If yes, how old were you when you were diagnosed with this condition?
3. What has/have been your primary occupation(s)?
4. Have you worked in jobs with significant dust exposure?
5. If yes, for how many years?
6. Do you currently take medicines for COPD?
7. If yes, which medicine(s) for COPD do you take?

C. Other Lung or Airway Disease:
1. Do you have any condition that may have affected your breathing or lung health, such as congenital conditions of the chest wall or spine (for example, scoliosis) or other conditions, such as sleep apnea?
2. Have you ever sustained any chest or lung injuries or trauma that have had a long-term impact on your breathing?
3. Have you had any medical issues affecting your heart, such as a heart attack or congestive heart failure, that have caused you to have shortness of breath or limited your ability to exercise?
4. Have you ever needed to be put on a mechanical ventilator or respirator for any reason?/If yes, was this needed for
5. Have there been any other illnesses, chronic conditions, injuries or anything you can think of in your past, even as a child, that may have had a lasting impact on your lungs or respiratory health?

Listing 16.2.4.12
Baseline Pulmonary Assessment **Part 2** - Pulmonary History

Treatment Group: Observational Cohort

Patient ID	A. Asthma Questions							B. COPD Questions							C. Other Lung or Airway Disease				
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5
xxxx-xxx	No							Yes	xx	xxx	No		No		Yes	No	xx	Yes./xxx	xx
xxxx-xxx	Yes/xxx	xxx	No	xx	xx	xxx	xxx	No											
...																			

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Programming note: The actual listing started with new page

Listing 16.2.4.13
Baseline Pulmonary Assessment Part 3 - **Assessments of Symptoms**

1. Shortness of breath or breathlessness? / If yes, when does this seem to occur?
2. Chest Tightness? / If yes, when does this seem to occur?
3. Chest Pain? / If yes, when does this seem to occur?
4. Persistent Cough? / If yes, when does this seem to occur?
5. Sputum Production/If yes, when does this seem to occur?
6. Episodes of coughing up blood or blood in your sputum?/ If yes, when does this seem to occur?

Listing 16.2.4.13
Baseline Pulmonary Assessment Part 3 - Assessments of Symptoms

Treatment Group: Observational Cohort

Patient ID	Assessments of Symptoms					
	1	2	3	4	5	6
xxxx-xxx	Yes,xxx	No	Yes,xxx	No	Yes,xxx	Yes,xxx
xxxx-xxx	No	Yes,xxx	Yes,xxx	Yes,xxx	No	No
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Programming note: The actual listing started with new page

Listing 16.2.5.1.1
Study Drug Administration: in Clinic and at Home

Treatment Group: CVT-301 (002/003)

Patient ID	Dosing Category	Visit	Start Date/Time of Treatment	End Date/Time of Treatment (Time 0)	Capsules Administered	Time Intervals	Doses/Day	Any Reinhalations/Which Capsules
	In Clinic				x	00:00 -< 00:30	x	No
xxxx-xxx		TV1	ddmonyyyyhh:mm	ddmonyyyyhh:mm				
	At Home	TV1-<TV2	ddmonyyyyhh:mm	ddmonyyyyhh:mm	x	00:30 -< 01:00	x	
		TV2-<TV2	ddmonyyyyhh:mm	ddmonyyyyhh:mm	x	01:00 -< 01:30	x	Yes/1st
		TV3-<TV4	ddmonyyyyhh:mm	ddmonyyyyhh:mm	x	01:30 -< 02:00	x	No
xxxx-xxx								
...								
Continue with CVT-301 (Naïve)								

Note: TV=Treatment;

Listing 16.2.5.1.2
Study Drug Administration: Derived Variables (in Clinic)

Treatment Group: CVT-301 (002/003)

Patient ID	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
xxxx-xxx	TV1	xx	xx	xx	x
	TV2	xx	xx	xx	x
	TV3	xx	xx	xx	x
	TV4	xx	xx	xx	x
					x
xxxx-xxx					
...					

Continue with CVT-301 (Naïve)

Note: TV=Treatment Visit;

Listing 16.2.5.1.3
Study Drug Administration: Derived Variables (Overall)

Treatment Group: CVT-301 (002/003)

Patient ID	Duration of Exposure (days) [a]	Total # of Capsules Taken	Average Daily Capsules	Total # of Doses Taken	Average Daily Dose(s)
xxxx-xxx	xx	xx	xx	xx	2
	xx	xx	xx	xx	3
	xx	xx	xx	xx	5
	xx	xx	xx	xx	4
	xx	xx	xx	xx	5
	xx	xx	xx	xx	4
	xx	xx	xx	xx	5
xxxx-xxx					
...					
Continue with CVT-301 (Naïve)					

[a] Duration of exposure (days) is calculated as documented last dose date-first dose date +1.

Listing 16.2.5.1.4
Study Drug Administration: Derived Variables (Overall by Visit)

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Total # of Capsules Taken	Average Daily Capsules	Total # of Doses Taken	Average Daily Dose(s)
xxxx-xxx	TV1-<TV2	xx	xx	xx	2
	TV2-<TV3	xx	xx	xx	3
	TV3-<TV4	xx	xx	xx	5
		xx	xx	xx	4
xxxx-xxx					
...					
Continue with CVT-301 (Naïve)					

Note: TV = Treatment Visit;

Listing 16.2.5.1.5
Listing of Study Drug Dose Change

Treatment Group: CVT-301 (002/003)

Patient ID	Type of change	Reason for Change	Date of Change	Old Dose Level (# capsules per treatment)	New Dose Level (# capsules per treatment)	Was Medical Monitor Contacted?
xxxx-xxx	Increase	xxxxx	ddmmmyyyy	1	2	Yes
xxxx-xxx	Decrease	xxxxxxxxxx	ddmmmyyyy	2	1	No
xxxx-xxx	Decrease	xxxxxxxxxx	ddmmmyyyy	2	1	Yes
...						
Continue with CVT-301 (Naïve)						

Listing 16.2.5.2
Study Drug Kit Dispensation

Patient ID	Visit	Treatment	Kit Number Dispensed	Date Dispensed
xxxx-xxx	TV1	Observational Cohort	xxxx	ddmonyyyy
	TV2	Observational Cohort	xxxx	ddmonyyyy
	TV3	Observational Cohort	xxxx	ddmonyyyy
	Other: xxxx	Observational Cohort	xxxx	ddmonyyyy
xxxx-xxx		CVT DL1		
...				

Note: TV=Treatment Visit; UNS= Unscheduled;

Listing 16.2.5.3
Daily Levodopa Dose

Treatment Group: Observational Cohort

Patient ID	Visit	How many times	Total Levodopa daily dose
xxxx-xxx	SV1	xx	
	TV1	xx	xxxx
	TV2	xx	xxxx
	TV3	xx	xxxx
	...		xxxx
xxxx-xxx			
...			

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; UNS= Unscheduled;

Listing 16.2.6.1.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 3

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Time Point	Date and Time of Assessment	Speech	Facial Exp.	Tremor at Rest					Action or Postural Tremor		Rigidity				
						Face	RUE	LUE	RLE	LLE	RUE	LUE	Neck	RUE	LUE	RLE	LLE
xxx-xxx	SV1 - OFF		16APR2013 14:10	1	1	0	0	0	0	0	0	0	3	3	1	1	1
	SV1 - ON		16APR2013 16:20	1	1	0	0	0	0	0	0	0	3	1	0	0	0
xxx-xxx	SV1 - OFF		16APR2013 15:35	2	2	0	0	0	0	2	1	1	1	1	1	0	0
	SV1 - ON		16APR2013 14:10	1	1	0	0	0	0	2	1	1	1	0	0	1	0
	SV2		Not Done, not applicable														
	TV1	Pre-dose	14MAY2013 11:20	2	2	0	0	0	0	0	1	1	2	1	1	0	0
		+10 mins	14MAY2013 11:37	0	1	0	0	0	0	0	0	0	2	0	0	0	0
		+20 mins	14MAY2013 11:47	1	0	0	0	0	0	0	0	0	1	0	0	0	0
		+30 mins	14MAY2013 11:57	0	1	0	0	0	0	0	0	0	2	0	0	0	0
		+60 mins	14MAY2013 12:27	2	1	0	0	0	0	0	0	1	2	1	0	0	0
	TV2	Pre-dose	21MAY2013 11:43	2	1	0	0	0	0	0	0	0	3	1	1	0	0

Continue with CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
*indicates imputed item score. 18=Speech, 19=Facial Expression, 20=Tremor at Rest, 21=Action or Postural Tremor of hands, 22=Rigidity, 23=Finger Taps, 24=Hand Movements, 25=Rapid Alternating Movements of Hands, 26=Leg Agility, 27=Arising from Chair, 28=Posture, 29=Gait, 30=Postural Stability, 31=Body Bradykinesia and Hypokinesia.

Listing 16.2.6.1.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 3

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Time Point	Date and Time of Assessment	Finger Taps		Hand Movements		Rapid Alternating Movements of Hands		Leg Agility		Arising from Chair
				Right	Left	Right	Left	Right	Left	Right	Left	
xxx-xxx	SV1 - OFF		16APR2013 14:10	4	2	2	2	3	2	1	1	4
	SV1 - ON		16APR2013 16:20	1	1	1	1	1	1	0	0	0
xxx-xxx	SV1 - OFF		16APR2013 15:35	2	1	1	0	1	0	1	1	0
	SV1 - ON		16APR2013 14:10	2	1	0	0	0	0	0	0	0
	SV2		Not Done, not applicable									
	TV1	Pre-dose	14MAY2013 11:20	2	2	2	1	1	1	0	1	0
		+10 mins	14MAY2013 11:37	1	1	0	1	1	1	0	0	0
		+20 mins	14MAY2013 11:47	0	1	1	1	0	0	0	2	0
		+30 mins	14MAY2013 11:57	0	0	1	1	0	1	0	0	0
		+60 mins	14MAY2013 12:27	1	2	1	1	1	1	1	2	0
	TV2	Pre-dose	21MAY2013 11:43	1	2	1	1	0	1	1	2	0

Continue with CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
*indicates imputed item score. 18=Speech, 19=Facial Expression, 20=Tremor at Rest, 21=Action or Postural Tremor of hands, 22=Rigidity, 23=Finger Taps, 24=Hand Movements, 25=Rapid Alternating Movements of Hands, 26=Leg Agility, 27=Arising from Chair, 28=Posture, 29=Gait, 30=Postural Stability, 31=Body Bradykinesia and Hypokinesia.

Listing 16.2.6.1.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 3

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Time Point	Date and Time of Assessment	Posture	Gait	Postural Stability	Bradykinesia/ Hypokinesia	UPDRS III Total Score
xxxx-xxx	SV1 - OFF		16APR2013 14:10	1	2	0	3	38
	SV1 - ON		16APR2013 16:20	1	1	0	2	16
xxx-xxx	SV1 - OFF		16APR2013 15:35	2	1	1	2	24*
	SV1 - ON		16APR2013 14:10	2	1	0	1	15
	SV2		Not Done, not applicable					
	TV1	Pre-dose	14MAY2013 11:20	1	1	0	2	24
		+10 mins	14MAY2013 11:37	1	1	0	1	11
		+20 mins	14MAY2013 11:47	1	1	0	1	10
		+30 mins	14MAY2013 11:57	1	1	0	1	9
		+60 mins	14MAY2013 12:27	2	1	0	1	21
	TV2	Pre-dose	21MAY2013 11:43	2	1	0	2	22

Continue with CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
*indicates imputed item score. 18=Speech, 19=Facial Expression, 20=Tremor at Rest, 21=Action or Postural Tremor of hands, 22=Rigidity, 23=Finger Taps, 24=Hand Movements, 25=Rapid Alternating Movements of Hands, 26=Leg Agility, 27=Arising from Chair, 28=Posture, 29=Gait, 30=Postural Stability, 31=Body Bradykinesia and Hypokinesia.

Listing 16.2.6.1.2
Unified Parkinson's Disease Rating Scale (UPDRS) Part 3: Derived Variables

Treatment Group: CVT-301 (002/003)

Patient ID	Visit	Time Point	UPDRS III Total Score	Change from Pre-dose	Mean Change from Pre-dose at 10 to 60 mins Post-dose	>=3 Reduction from Pre-dose	>=6 Reduction from Pre-dose	>=11 Reduction from Pre-dose
xxxx-xxx	TV2	Pre-dose	xx		xx			
		+10mins	xx	xx				
		+20mins	xx	xx			Y	
		+30mins	xx	xx		Y		Y
		+60mins	xx	xx		Y		
	TV3	Pre-dose	xx		xx			
		+10mins	xx	xx				
		+20mins	xx	xx				
		+30mins	xx	xx				
		+60mins	xx	xx				
	TV4	Pre-dose	xx		xx			
		+10mins	xx	xx				
		+20mins	xx	xx				
		+30mins	xx	xx				
		+60mins	xx	xx				
xxxx-xxx								
...								

Continue with CVT-301 (Naïve)

Note: TV = Treatment Visit; ET = Early Termination;

Listing 16.2.6.2.1
Clinic Assessment

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Time of Standard Morning Dose of LD-Containing Medications	Motor State at Arrival	Time Patient Turned OFF	Turned ON within the 60-min Post Dose Period?	Was Patient ON at 60-min Post Inhaled Treatment?	Experience Dyskinesia	Maximum Severity
xxxx-xxx	SV1	ddmonyyyy	hh:mm						
	SV2	Not Done, xxxx							
	TV1	ddmonyyyy	hh:mm	OFF	hh:mm	Yes	No	Yes	xxx
	…	ddmonyyyy	hh:mm	OFF	hh:mm	Yes	Yes	No	
xxxx-xxx									
...									

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; FU = Follow up; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.6.2.2
Parkinson's Disease Diary Data

Treatment Group: Observational Cohort

Patient ID	Week	Date of Assessment	Time of Assessment	Asleep	OFF	ON without Dyskinesia	ON with Non-troublesome Dyskinesia	ON with Troublesome Dyskinesia
xxxx-xxx	SV	ddmonyyyy	hh:mm					
	TV3	Not Done, xxxx						
	TV4	ddmonyyyy	hh:mm	1	0	0	0	0
	…	ddmonyyyy	hh:mm	1	0	0	0	0
xxxx-xxx								
...								

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; FU = Follow up; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.6.2.3.1

Parkinson's Disease Diary Data – Derived Variable by Dairy Date

Treatment Group: Observational Cohort

Patient ID	Visit	**Date of Assessment**	**Daily Awake Time (Hrs)**	Daily OFF Time (Hrs)/ **% of OFF time**	Daily ON Time Without Dyskinesia (hours)	Daily ON Time With Non-troublesome Dyskinesia (hours)	Daily ON Time With Troublesome Dyskinesia (hours)
xxxx-xxx	SV	ddmonyyyy	x.x	x.x	x.x	x.x	x.x
	TV2	ddmonyyyy	x.x	x.x	x.x	x.x	
	TV3	ddmonyyyy	x.x	x.x	x.x	x.x	x.x
	TV4	ddmonyyyy	x.x	x.x	x.x	x.x	x.x
xxxx-xxx							
...							

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; FU = Follow up; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.6.2.3.2

Parkinson's Disease Diary Data – Derived Variable by Visit

Treatment Group: Observational Cohort

Patient ID	Visit	**Date of Assessment**	**Daily Awake Time (Hrs)**	Mean Daily OFF Time (Hrs)/ **% of OFF time**	Mean Daily ON Time Without Dyskinesia (hours)	Mean Daily ON Time With Non-troublesome Dyskinesia (hours)	Mean Daily ON Time With Troublesome Dyskinesia (hours)	Baseline Daily OFF Time/ Category at Screening
xxxx-xxx	SV	ddmonyyyy	x.x	x.x	x.x	x.x	x.x	x.x /<4.5 hours
	TV2	ddmonyyyy	x.x	x.x	x.x	x.x		
	TV3	ddmonyyyy	x.x	x.x	x.x	x.x	x.x	
	TV4	ddmonyyyy	x.x	x.x	x.x	x.x	x.x	
xxxx-xxx								
...								

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; FU = Follow up; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.6.2.4
Patient's Global Impression of Change (PGI-C)

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Assessment	Response [a]
xxxx-xxx	TV4	ddmonyyyyhh:mm	x
xxxx-xxx	TV4	Ddmonyyyyhh:mm	x
xxxx-xxx			
...			

Note: TV = Treatment Visit; [a] 1 = Much Improved, 2 = Improved, 3 = A little Improved, 4 = No change, 5 = A little worse, 6 = Worse, 7 = Much worse.

Listing 16.2.6.2.5
Impact of Parkinson's OFF Episodes

Time Spend in OFF Time:
1. Over the last week, on average… how many hours in the day are you typically awake?
2. Over the last week, on average… how many of your awake hours are typically in an OFF state?
3. Over the last week, on average… how many OFF episodes do you experience in a typical day?
4. Over the last week, on average… what is the typical duration of each OFF episode?

Functional Impact of OFF time
1. Over the last week, on average, when you experience an OFF episode, did it stop you from doing things?

Impact of OFF Time on Activities of Daily Living
a. Motor and Physical
  1. Had difficulty with housework or cooking?
  2. Had difficult with work tasks like typing?
  3. Had difficulty getting around in public?
  4. Been confined to the house more than you would like?
  5. Had difficulty washing/dressing yourself?
  6. Felt Pain?
  7. Had difficulty walking safely?
b. Social and Cognitive
  1. Felt depressed?
  2. Felt anxious?
  3. Had problems with concentration?
  4. Felt memory was bad?
  5. Felt unable to communicate properly?
  6. Had trouble mentally changing from one task to another?
c. Any other things you would like to share about your off time

Impact of OFF Time on Well-being and quality of Life
1. Over the last week, on average, how do OFF periods affect your overall feeling of health and well-being?

Impact of OFF Time on Disability
1. Over the last week, on an average day when you are in an ON state, you would rate your disability:
2. Over the last week, on an average day when experiencing OFF time, you would rate your disability:

Listing **16.2.6.2.5**
Impact of Parkinson's OFF Episodes

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Time Spend in OFF Time				Impact of OFF Time on Activities of Daily Living											
							Motor and Physical							Social and Cognitive				
			1	2	3	4	1	2	3	4	5	6	7	1	2	3	4	5	6
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
xxxx-xxx	TV1		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
...																			

Note: TV = Treatment Visit;
Programming note: The actual listing started with new page

Listing 16.2.6.2.5
Impact of Parkinson's OFF Episodes

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Functional Impact of OFF time	Impact of OFF Time on Well-being and Quality of Life	Impact of OFF Time on Disability		Any other things you would like to share about your OFF time
			1		1	2	
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	xxxx
xxxx-xxx	TV1		x	x	x	x	xxxxx
...							

Listing 16.2.6.3.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 2

Treatment Group: Observational Cohort

Patient ID	Visit	Date Of Assessment	5	6	7	8	9	10	11	12	13	14	15	16	17	Total Score	Change from Baseline
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	TV4	Not Done, xxx															
	...																
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	TV4	ddmonyyyy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; ET = Early Termination;
5=Speech, 6=Salivation, 7=Swallowing, 8=Handwriting, 9=Cutting food and handling utensils, 10=Dressing, 11=Hygiene, 12=Turning in bed and adjusting bed clothes, 13=Falling(unrelated to freezing), 14=Freezing when walking, 15=Walking, 16=Tremor(Symptomatic complaint of tremor in any part of body), 17=Sensory complaints related to parkinsonism.

Listing 16.2.6.3.2
Listing of S&E Activities of Daily Living

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Rating Description of ADL capability
xxxx-xxx	TV1	ddmonyyyy	x
	TV4	ddmonyyyy	x
xxxx-xxx	TV1	ddmonyyyy	x
	TV4	Not Done, xxxxxxxx	
xxxx-xxx			
...			

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; ET = Early Termination;

Listing 16.2.6.3.3
39 Item Parkinson's Disease Questionnaire (PDQ-39)

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Assessment	Mobility										Dimension Score
			1	2	3	4	5	6	7	8	9	10	
xxxx-xxx	TV1	ddmonyyyyhh:mm	x	x	x	x	x	x	x	x	x	x	x
	TV4	Not Done, xxxxx											
	...												
xxxx-xxx													
...													
Continue with CVT-301 (002/003), CVT-301 (Naïve)													

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
The assessments on TV1 were taken prior to study medication application.

Listing 16.2.6.3.3
39 Item Parkinson's Disease Questionnaire (PDQ-39)

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Assessment	Activities of Daily Living							Emotional Well-being						
			11	12	13	14	15	16	Dimension Score	17	18	19	20	21	22	Dimension Score
xxxx-xxx	TV1	ddmonyyyyhh:mm	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	TV4	Not Done, xxxxx														
	...															
xxxx-xxx																
...																

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
The assessments on TV1 were taken prior to study medication application.

Listing 16.2.6.3.3
39 Item Parkinson's Disease Questionnaire (PDQ-39)

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Assessment	Stigma					Social Support				Cognitions				
			23	24	25	26	Dimension Score	27	28	29	Dimension Score	30	31	32	33	Dimension Score
xxxx-xxx	TV1	ddmonyyyyhh:mm	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	TV4	Not Done, xxxxx														
	...															
xxxx-xxx																
...																

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
The assessments on TV1 were taken prior to study medication application.

Listing 16.2.6.3.3
39 Item Parkinson's Disease Questionnaire (PDQ-39)

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Assessment	Communication				Bodily Discomfort				Summary Index Score
			34	35	36	Dimension Score	37	38	39	Dimension Score	
xxxx-xxx	TV1	ddmonyyyyhh:mm	x	x	x	x	x	x	x	x	x
	TV4	Not Done, xxxxx									
	...										
xxxx-xxx											
...											

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;
The assessments on TV1 were taken prior to study medication application.

Listing 16.2.7.1
Adverse Events

Treatment Group: Observational Cohort

Patient ID	System Organ Class/ Preferred Term/ Verbatim Term [a]	AE Start Date and Time/ Study Day [b]	AE Stop Date and Time	I: Intensity R: Relationship to Study Medication A: Action Taken	Outcome	SAE? If Yes, Specify [c]
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/	ddmonyyyy	R: xxxxxxxx		
xxxx-xxx	xxxxxxxxx	-xx	Hh:mm	A: xxxxxxxxx	Resolved	Yes: 1
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/		R: xxxxxxxx		
	xxxxxxxxx	xx#	Ongoing	A: xxxxxxxxx	Unknown	No
	xxxxxxxxxx/	ddmonyyyy		I: xxxxxxxx		
	xxxxxxxxx/	hh:mm/	ddmonyyyy	R: xxxxxxxx		
xxxx-xxx	xxxxxxxxx	-xx	Hh:mm	A: xxxxxxxxx	Resolved	Yes: 2
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Notes: TEAE=Treatment-emergent AE. SAE=Serious AE.[a] Adverse events were coded into system organ class and preferred term using MedDRA version 17.0.
[b] TEAEs were flagged with a #. The AEs occurred on the clinic visit were flagged with *.Study day is relative to date of first study medication (date of first dose = Day 1).
[c] 1 = The event is fatal or life-threatening, 2 = The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns), 3 = The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization, 4 = The event is a congenital anomaly, 5 = The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

Listing 16.2.8.1.1
Clinical Laboratory Results - Hematology

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Sample	Test1 unit	Test2 unit	Test3 unit	...
xxxx-xxx	SV1	ddmonyyyyhh:mm	xx H*	xx L*	xx	
	TV1	ddmonyyyyhh:mm	xx	xx	xx	
	TV4	Not Done, xxxxx	xx H**	xx H**	xx	
xxxx-xxx						
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled;
L = Low, H = High, L* = potentially clinically significant (PCS) low value, H* = PCS high value,
L** = potentially clinically significant change (PCSC) low, H** = PCSC high.

Below listing will has similar structure as Listing 16.2.8.1.1

Listing 16.2.8.1.2
Clinical Laboratory Results – Chemistry

Listing 16.2.8.1.3
Serum Pregnancy Test – Positive Only

Treatment Group: Observational Cohort

Patient ID	Visit	Date and Time of Sample	Result
xxxx-xxx	SV1	ddmonyyyyhh:mm	Positive
	TV1	ddmonyyyyhh:mm	Positive
xxxx-xxx	SV1		
	...		
xxxx-xxx	SV1		
	...		
...			

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled; At home pregnancy tests and an extra serum pregnancy test at TV2 visit will be performed for the CVT treated patients in Belgium and Germany.

Listing 16.2.8.2.1
Vital Signs

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Date and Time Of Assessment	Position	Blood Pressure (mmHg) SBP	Blood Pressure (mmHg) DBP	Heart Rate (beats per minute)	Respiration Rate (breaths per minute)
xxxx-xxx	SV1		ddmonyyyyhh:mm	Standing Supine/Semi-Supine	xx	xx	xx	xx
	TV1	Pre-dose	ddmonyyyyhh:mm		xx	xx	xx	xx
		+5mins			xx H*	xx L**	xx	xx
		...	Not Done, xxxxx					
xxxx-xxx								
...								

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled;
L* = potentially clinically significant (PCS) low value, H* = PCS high value,
L** = potentially clinically significant change (PCSC) low, H** = PCSC high.

Listing 16.2.8.2.2
12-Lead Electrocardiogram (ECG)

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Date and Time Of Assessment	Heart Rate (bpm)	RR (ms)	PR (ms)	QRS (ms)	QT (ms)	QTcB (ms)	QTcF (ms)	Result
xxxx-xxx	SV1		ddmonyyyyhh:mm	xx	xx	xx	xx	xx	xx	xx	Normal
	TV1	Pre-dose	ddmonyyyyhh:mm	xx	xx	xx	xx	xx	xx	xx	Normal
		+5mins	Not Done	xx	xx	xx L**	xx	xx H**	Xx	xx	Abnormal CS
		+20mins									Abnormal NCS
		+30mins									
		...									
	...										
xxxx-xxx											
...											

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled;
L* = potentially clinically significant (PCS) low value, H* = PCS high value,
For PR interval, H1= PCSC high, >25% for baseline >=200; H2= PCSC high, >25% for baseline >=200; For QRS interval, H1= PCSC high, >25% for baseline >=100; H2= PCSC high, >25% for baseline >=100; For QTcB and QTcF, H1**=PCSC high, >15% for baseline >=440 ; H2**=PCSC high, >30% for baseline <440; H3**=PCSC high, Increase>30; H4**=PCSC high, Increase>60, H5**=PCSC high Change>30 and Value>500, H6**=PCSC high, Change>60 and Value>500

Listing 16.2.8.2.3
Physical Examination

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Any Clinically Significant Abnormal Findings That Are New or Have Worsened?	Findings
xxxx-xxx	SV1	ddmonyyyy	Yes	New or Worsened Clinically Significant
	SV2	Not Done		
	TV1	ddmonyyyy	...	
	…			
xxxx-xxx				
...				

Continue with CVT-301 (002/003), CVT-301 (Naïve)

SV = Screening Visit; TV=Treatment Visit; FU= Follow-up; UNS= unscheduled;
[a] BMI was calculated as weight (kg) / [height (m)]^2.

Listing 16.2.8.2.4.1
Spirometry(Neurology Office)

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Motor State	Date and Time of Assessment	FEV1 (Liter)	FEV1 (% Predicted)	FVC (Liter)	FVC (% Predicted)	FEV1/FVC (%)
xxxx-xxx@	Screening		ON	ddmonyyyyhh:mm	xx	xx	xx	xx	xx
	TV1	Arrival	ON	ddmonyyyyhh:mm #	xx	xx	xx	xx	xx
		Pre-dose		ddmonyyyyhh:mm	xx	xx	xx	xx	xx
		+15mins		ddmonyyyyhh:mm	Xx *	Xx $	xx	xx	xx
		...		Not Done, xxx					

xxxx-xxx

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; # indicates spirometry measurement not meeting ATS quality criteria. * indicates imputed values. $ indicates manual data @ indicates patients with Co-efficient of Variation (CV) of FEV1 >7.5%

Listing 16.2.8.2.4.2
Spirometry(Neurology Office) Measurements Not Meeting ATS Quality Criteria

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Motor State	Date and Time of Assessment	Acceptable Efforts	Repeatable Efforts
xxxx-xxx@	SV		ON	ddmonyyyyhh:mm #	x	x
	TV1	Arrival	ON	ddmonyyyyhh:mm #	x	x
		Pre-dose		ddmonyyyyhh:mm #	x	x
		...				
xxxx-xxx						
...						

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; # indicates spirometry measurement not meeting ATS quality criteria. @ indicates patients with Coefficient of Variation (CV) of FEV1 >7.5%

Listing 16.2.8.2.4.3
Spirometry(Pulmonary Function Facility): DLco Parameters

Treatment Group: Observational Cohort

Patient ID	Visit	Time Point	Motor State	Date and Time of Assessment	1/20/21	2	3	4(13)/7(15)	5(14)/8(16)	6/9	10	
xxxx-xxx@	Screening		ON	ddmonyyyyhh:mm				xx	xx	xx	xx	xx
		Arrival	ON	ddmonyyyyhh:mm				xx	xx	xx	xx	xx
	TV1			#								
		Pre-dose		ddmonyyyyhh:mm				xx	xx	xx	xx	xx
		+15mins		ddmonyyyyhh:mm				Xx *	Xx $	xx	xx	xx
		...		Not Done, xxx								

xxxx-xxx

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; # indicates spirometry measurement not meeting ATS quality criteria. $ indicates manual data @ indicates patients with Co-efficient of Variation (CV) of FEV1 >7.5%; 1=DLCO (mL/min/mmHg), 2=IVC (L), 3=VA (L), 4=Pre Original FEV1 (L), 5=Pre Original FVC (L), 6=Pre FEV1/FVC (%),7=Post Original FEV1, 8=Post Original FVC, 9=Post FEV1/FVC (%),10=SVC (L), 13=Percentage Predicted Pre-FEV1 (%),14=Percentage Predicted Pre-FVC (%), 15=Percentage Predicted Post-FEV1 (%) , 16=Percentage Predicted Post-FVC (%), 20=Percentage Predicted DLCO (%)

Listing 16.2.8.2.4.4
Spirometry(Pulmonary Function Facility): Spirometry/DLco Measurements Not Meeting ATS Quality Criteria

Will have same format as L16.2.8.2.4.3 **and removed the irrelevant columns (**Motor State, Repeatable Efforts and Acceptable Efforts**)**

# indicates DLco measurement not meeting ATS quality criteria.

Listing 16.2.8.2.5
Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicide Ideation:
1.Wish to be Dead
2.Non-Specific Suicidal Thought
3.Suicidal Ideation-No Intent
4.Ideation With Intent, No Plan
5.Ideation With Plan/Intent

Intensity of Ideation:
1.Most Severe Ideation
2.Most Severe Ideation, Description
3.Most Severe Ideation, Frequency
4.Most Severe Ideation, Duration
5.Most Severe Ideation, Control
6.Most Severe Ideation, Deterrents
7.Most Severe Ideation, Reasons

Suicidal Behavior:
1.Actual Attempt
2.Number of Actual Attempts
3.Non-suicidal Self-injurious Behavior
4.Interrupted Attempt
5.Number of Interrupted Attempts
6.Aborted Attempt
7.Number of Aborted Attempts
8.Preparatory Acts/Behavior
9.Suicidal Behavior
10.Completed Suicide

Actual Attempts:
1.Most Recent Attempt Date
2.Most Recent Attempt Damage
3.Most Recent Attempt Potential
4.Most Lethal Attempt Date
5.Most Lethal Attempt Damage
6.Most Lethal Attempt Potential
7.First Attempt Date
8.First Attempt Damage
9.First Attempt Potential

Listing 16.2.8.2.5
Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Suicide Ideation					Intensity of Ideation						
			1	2	3	4	5	1	2	3	4	5	6	7
xxxx-xxx	TV1	ddmonyyyy												
	TV4	Not Done, xxxxxx												
xxxx-xxx														
...														

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;
Programming note: The actual listing started with new page

Listing 16.2.8.2.5
Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Suicidal Behavior 1	2	3	4	5	6	7	8	9	10
xxxx-xxx	TV1	ddmonyyyy										
	TV4	Not Done, xxxxxx										
xxxx-xxx												
...												

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;

Listing 16.2.8.2.5
Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	Actual Attempts 1	2	3	4	5	6	7	8	9
xxxx-xxx	TV1	ddmonyyyy									
	TV4	Not Done, xxxxxx									
xxxx-xxx											
...											

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;

Listing 16.2.8.2.6
Epworth Sleepiness Scale

Treatment Group: Observational Cohort

Patient ID	Visit	Date of Assessment	1	2	3	4	5	6	7	8	Total Score
xxxx-xxx	TV1	ddmonyyyy	xx	xx	xx	xx	xx	xx	xx	xx	xx
	TV4	Not Done, xxxxxxx									
xxxx-xxx											
...											

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit; 1 = Sitting and reading, 2 = Watching TV, 3 = Sitting inactive in a public place, 4 = As a passenger in a car for an hour
without a break, 5 = Lying down to rest in the afternoon when circumstances permit, 6 = Sitting and talking to someone,
7 = Sitting quietly after a lunch without alcohol, 8 = In a car, while stopped for a few minutes in traffic.

Listing 16.2.8.2.7
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (QUIP)

Treatment Group: Observational Cohort

			Impulse control disorders									
Patient ID	Visit	Date of Assessment	1. Gambling	1. Sex	1. Buying	1. Eating	2. Gambling	2. Sex	2. Buying	2. Eating	3. Gambling	3. Sex
xxxx-xxx	TV1	ddmonyyyy	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	TV4	Not Done, xxxxxxx										
xxxx-xxx												
...												

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;

Listing 16.2.8.2.7
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (QUIP)

Treatment Group: Observational Cohort

			Impulse control disorders									
Patient ID	Visit	Date of Assessment	3. Buying	3. Eating	4. Gambling	4. Sex	4. Buying	4. Eating	5. Gambling	5. Sex	5. Buying	5. Eating
xxxx-xxx	TV1	ddmonyyyy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	TV4	Not Done, xxxxxxx										
xxxx-xxx												
...												

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;

Listing 16.2.8.2.7
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's (QUIP)

Treatment Group: Observational Cohort

			Other compulsive behaviors					Compulsive medication use				
Patient ID	Visit	Date of Assessment	1A	1B	1C	2	3	1	2	3	4	5
xxxx-xxx	TV1	ddmonyyyy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	TV4	Not Done, xxxxxxx										
xxxx-xxx												
...												

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: TV = Treatment Visit;

Listing 16.2.8.2.8.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 4

Dyskinesias:
32. Duration: What proportion of the waking day are dyskinesias present?
33. Disability: How disabling are the dyskinesias?
34. Painful Dyskinesias: How painful are the dyskinesias?
35. Presence of Early Morning Dystonia.

Clinical Fluctuations:
36. Are "off" periods predictable?
37. Are "off" periods unpredictable?
38. Do "off" periods come on suddenly, within a few seconds?
39. What proportion of the waking day is the patient "off" on average?

Other Complications:
40. Does the patient have anorexia, nausea, or vomiting?
41. Any sleep disturbances, such as insomnia or hypersomnolence?
42. Does the patient have symptomatic orthostasis?

Listing 16.2.8.2.8.1
Unified Parkinson's Disease Rating Scale (UPDRS) Part 4

Treatment Group: Observational Cohort

			Dyskinesias				Clinical Fluctuations				Other Complications		
Patient ID	Visit	Date Of Assessment	32	33	34	35	36	37	38	39	40	41	42
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	x	x	x	x	x*	x	x
	TV4	Not Done, xxx											
	...												
xxxx-xxx	TV1	ddmonyyyy	x	x	x	x	x	x*	x	x	x	x	x
	TV4	ddmonyyyy	x	x	x	x	x	x	x	x	x	x*	x

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.8.2.8.2
Unified Parkinson's Disease Rating Scale (UPDRS) Part 4: Derived Variables

Treatment Group: Observational Cohort

Patient ID	Score Category	Visit	Change from Baseline	Percent change from Baseline
xxxx-xxx	Total Score	TV1		
		TV4	xx	xx.xx
	Dyskinesias	TV1		
		TV4	xx	xx.xx
	Clinical Fluctuations	TV1		
		TV4	xx	xx.xx
xxxx-xxx				

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Note: SV = Screening Visit; TV = Treatment Visit; ET = Early Termination; UNS = Unscheduled;

Listing 16.2.8.2.9.1
Telephone Contact

Treatment Group: Observational Cohort

Patient ID	Date of Contact	Any Changes to PD Medications?	Any Challenges with Inhaler or Capsules?	Any Challenges with Diary?	Any Adverse Events Noted?
xxxx-xxx	ddmonyyyy	Yes	No	No	Yes
	ddmonyyyy	Yes	Yes, xxxxxxxxxx	Yes, xxxxxxxxxx	Yes
	...				
xxxx-xxx					
...					

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Listing 16.2.8.2.9.2
Telephone Contact: Challenges with Inhaler or Capsules Data

Treatment Group: Observational Cohort

Patient ID	Date of Contact	Any Changes to PD Medications?	Any Challenges with Inhaler or Capsules?	Any Challenges with Diary?	Any Adverse Events Noted?
xxxx-xxx	ddmonyyyy	No	Yes, xxxxxxxxxx	No	Yes
	ddmonyyyy	Yes	Yes, xxxxxxxxxx	Yes, xxxxxxxxxx	Yes
	...				
xxxx-xxx					
...					

Continue with CVT-301 (002/003), CVT-301 (Naïve)

Statistical Analysis Plan

Study No. CVT-301-005 Summary of SAP Changes From final Version 1.0 (22-Dec-2015) to Version 2.0 (13Jan2017)	
SAP final version 1.0 (22-Dec-2015)	SAP final version 2.0 (13Jan2017)
Cover page: CVT-301-005 A Phase 3, Randomized Study Investigating the Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control (SUPPORT-PD™) Protocol Version and Date: Version 3.0 19-Aug-2015; SAP version and date: Final version 1.0, 22-Dec-2015	Cover page: CVT-301-005 A Phase 3, Randomized Study Investigating the Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control Protocol Version and Date: Version 4.0, 07-Mar-2016 SAP version and date: Final version 2.0, 13-Jan-2017
3.5 Determination of Sample Size Approximately 250 CVT-301 treatment patients and 115 control patients will be enrolled in this study. It is assumed that the drop-out rate will be approximately 25%.	3.5 Determination of Sample Size Approximately 350 CVT-301 treatment patients and 175 control patients will be enrolled in this study.

The primary objective of this study will be to characterize the pulmonary safety within the CVT-301-treated patients and the differences between the groups will be estimated as a secondary objective. However, for the secondary comparison of FEV1 change between the CVT-301 treatment group and the randomized observational cohort, the standard deviation of FEV1 change from baseline is expected to be 0.281 L, based on data from Study CVT-301-003. Assuming that there is no difference in the changes from baseline between the CVT-301-treated patients and the observational cohort, the study has the following power for the comparison between the 2 groups. The upper limit of the 95% confidence interval for the difference between the 2 groups in change from baseline in FEV1 will be less than 0.121 L with 90% power, assuming 188 and 86 patients completing the study in the CVT-301 treatment group and observational cohort, respectively. The sample size calculation was performed using nQuery Advisor, Version 7.0.	
	3.6 Treatment Assignment & Blinding Add sentence below: Randomization can occur before the baseline DLco has been performed. Note: Patients who were enrolled from the CVT-301-002 and CVT-301-003 studies under an earlier version of this protocol (Version 2) were assigned only to the CVT-301 treatment group.
5.2 Safety population The Safety Population will include all randomized	5.2 Safety population The Safety Population will include all randomized

patients who received at least 1 dose of inhaled CVT-301 and patients from the Observational Cohort. Patients will be analyzed according to study treatment that they received. The Safety Population will be used for all analyses of safety endpoints and summaries of patient demographics and baseline characteristics.	patients who received at least 1 dose of inhaled CVT-301 and patients from the Observational ***Cohort who came in for treatment visit 1.*** Patients will be analyzed according to study treatment that they received. The Safety Population will be used for all analyses of safety endpoints and summaries of patient demographics and baseline characteristics.
6.2 Key Definitions *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 in)* • *Women predicted DLCO = 2.2382 - (0.1111 x age) + (0.4068 x height in)* Where age is the age ***at the time of assessment taken***,	6.2 Key Definitions 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 in)* • *Women predicted DLCO = 2.2382 - (0.1111 x age) + (0.4068 x height in)* Where age is the age ***at baseline***, height is measured in

height is measured in inches.	inches.
8.1 Spirometry Spirometry will be performed by trained and qualified staff at each study site. 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. FEV1, FVC, FEV1/FVC ratio and DLco will be summarized descriptively by treatment group and overall. For screening data, the summary will be presented for each motor status, ON or OFF, separately. For other visits, data in ON or OFF state will be combined for summary. The following will be summarized: • ***Change from baseline to other visits Arrival values for each parameter. The baseline is defined as the***	8.1 Spirometry Spirometry will be performed by trained and qualified staff at each study site. 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 %***

TV/OV1 Arrival value. If the TV/OV1 Arrival value is missing, the last available value in ON state before the first dose of study drug will be used. • 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 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 classified as not meeting the criteria for acceptability, not meeting the criteria for repeatability or as other/unknown and summarized.*** ***The spirometry analyses*** will be repeated for the subset of assessments meeting the ATS quality criteria. Another subset analysis will be performed by excluding the ***spirometry*** data from … In addition to the descriptive statistics, the changes in the	***of Hb adjusted predicted DLCO will be summarized descriptively by treatment group and overall.*** • ***Change from baseline to other visits for each parameter. The summary for FEV1 will also be provided by smoker status.*** • 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 …

spirometry values within …	In addition to the descriptive statistics, the changes in the ***FEV1, FEV1/FVC ratio, and DLCO*** values within …
Sensitivity analyses of the spirometry data	**Sensitivity analyses of the spirometry data**
The following sensitivity analysis will be performed for the ***primary endpoint***.	The following sensitivity analysis will be performed for the ***FEV1, FVC/FEV1 and DLCO assessments***.
	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 TV/OV1 Arrival value. If the TV/OV1 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.***

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-301-005 A Phase 3, Randomized Study Investigating the Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control
Protocol Version and Date:	Version 4.0, 07-Mar-2016
INC Research Project Code:	[redacted]
Author(s):	[redacted]
SAP Version:	Final Version 2.0
SAP Version Date:	13-Jan-2017

Statistical Analysis Plan

Version: Final Version 2.0 **Version Date:** 13-Jan-2017

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

APPROVALS
INC Research
[redacted]
[redacted]
[redacted]
[redacted]

Statistical Analysis Plan

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Statistical Analysis Plan

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
BMI	Body Mass Index
BMS	Biomedical Systems
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
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
Hb	hemoglobin
HR	Heart Rate

Statistical Analysis Plan

Abbreviation	Description
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LD	Levodopa
LS	least square
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
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
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

Statistical Analysis Plan

Abbreviation	Description
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 database lock. However, because this is an open-label study, the analyses defined after the first patient has been randomized to the study 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

- To characterize the pulmonary safety, as assessed by spirometry (FEV1, FVC and FEV1/FVC ratio), over a 12-month period in the observational ('standard of care') cohort.

- To estimate the difference between the CVT-301-treated patients and the observational cohort on measures of pulmonary safety.

- To characterize the effects of CVT-301 on safety over a 12-month period: safety will be assessed by adverse event (AE) reports, physical examination, standard and orthostatic vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), clinical laboratory tests, 12-lead electrocardiograms (ECGs), the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP), the Epworth Sleepiness Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

- To evaluate the effect of CVT-301 on mean change from baseline in the UPDRS Part 4 measures of motor fluctuations (dyskinesias [Q32-35] and wearing off [Q36-39]) measured at baseline and at 6 and 12 months after the initiation of CVT-301 treatment.

- To characterize the occurrence and severity of examiner-rated dyskinesia following treatment of patients experiencing an OFF episode in the clinic over a 12-month period.

- To describe the effects of CVT-301 on Carbon Monoxide Diffusion Capacity (DLCO) over a 12-month period.

3.3. EXPLORATORY EFFICACY OBJECTIVES

The following exploratory objectives related to the efficacy endpoints will primarily be assessed for the CVT-301-treated patients. The same objectives will be explored for the pool of CVT-301-naïve patients and patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies, if feasible.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode.
- Time curves of the UPDRS response at 10, 20, 30 and 60 minutes will be evaluated descriptively
- Change from pre-dose in the average UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode.
- Proportion of patients with a ≥ 3, ≥ 6, and ≥ 11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10, 20, 30, and 60 minutes.
- Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic, maintaining the ON state at 60 minutes after study drug administration (per the examiner's subjective assessment).
- 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 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.
- Change from baseline in Schwab and England (S&E) Activities of Daily Living (ADL).
- Change from baseline in UPDRS Part 2 score.

3.4. PATIENT SELECTION

The study population for this study is PD patients experiencing motor fluctuations (OFF episodes) that meet the following inclusion criteria and do not meet any of the following exclusion criteria.

Patients may have been previously enrolled in the CVT-301-002 or CVT-301-003 studies, or may be CVT-301-naïve i.e. no previous exposure to CVT-301. Patients previously enrolled in the CVT-301-002 and CVT-301-003 studies must have completed all of the CVT-301 study visits without any safety issues that would preclude participation in this study according to the investigator. Patients who withdrew from either of the CVT-301 studies prior to completion, for any reason, will not be eligible.

3.4.1. Inclusion Criteria

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 85 years, inclusive. Women of child-bearing potential must use protocol-defined contraceptive measures (see Section 11.1.5) and must have a negative serum human chorionic gonadotropin (hCG) test at screening. These patients must be willing to remain on their current form of contraception for the duration of the study.
- Patients who have idiopathic PD (i.e., not induced by drugs or other diseases) as defined by fulfilling Steps 1 and 2 of the UK Brain Bank criteria, diagnosed after the age of 30 years.
- Patients who are classified as Stage 1 to 3 (in the ON state) on the modified Hoehn and Yahr scale for staging of PD severity.
- Patients who have experienced motor fluctuations for a minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) by self-report and confirmed by the PD Diary (on 3 consecutive days) during the screening period.
- Patients who are on a LD-containing therapy, not including Rytary (or equivalent), must be stable on oral LD-containing therapy for at least 2 weeks prior to SV1 with a LD/dopamine decarboxylase inhibitor (DDI)-containing regimen.
- Patients who are on a LD containing therapy, when including Rytary (or equivalent), should be on a stable dose for at least 6 weeks prior to SV1
- The frequency of L-dopa administrations must be at least 3 times during the waking day and a total daily LD dose of ≤1600 mg (exclusive of PRN LD-containing medications).
- Patients should be stable on other PD medications for at least 4 weeks prior to SV1.

- Patients must have a ≥ 25% difference between UPDRS Part 3 scores recorded in their ON and OFF states at screening.

- Patients must have normal cognition as confirmed by a score of ≥ 25 on the MMSE.

- Patients must be able to perform a spirometry maneuver in the ON and OFF states, and must have a screening FEV1 ≥ 50% of predicted and an FEV1/FVC ratio >60% in the ON state at screening. (A pulmonologist will review the spirometry tracings/morphology of any patient with an FEV1 that is ≥ 50% to <60% of predicted or an FEV1/FVC ratio that is >60% to <70% in order to determine potential eligibility. All CVT-301-naïve patients with an FEV1/FVC ratio of >60% to <70% will be required to undergo a bronchodilator challenge and the results must be reviewed prior to entry into the study. Patients with an FEV1/FVC ratio that is >60% to <70% will complete spirometry before and after the administration of a bronchodilator in a pulmonary function laboratory. Testing will be performed in accordance with the 2005 ATS/European Respiratory Society [ERS] criteria prior to randomization. The results of the bronchodilator challenge will be reviewed by a pulmonologist prior to potential randomization.)

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 deep brain stimulation [DBS] or cell transplantation).

- Patients with a history of psychotic symptoms requiring treatment, or suicide ideation or attempt within the prior 12 months (stable regimens [for at least 4 weeks prior to SV1] of anti-depressant and certain low-dose atypical antipsychotic medications are permitted, in case they are indicated to treat symptoms other than psychotic symptoms).

- Patients who have cancer with the exception of the following: basal cell carcinoma or successfully treated squamous cell carcinoma of the skin; cervical carcinoma in situ; prostatic carcinoma in situ; or other malignancies curatively treated and with no evidence of disease recurrence for at least 3 years.

- Patients taking certain prohibited medications (see Section 9.4.2).

- Patients with a history of drug or alcohol abuse within the prior 12 months.

- Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years.

- Patients with any contraindication to performing routine spirometry or who are unable to perform a spirometry maneuver (see Appendix 20 for a list of contraindications).

- Patients with a current history of *symptomatic* orthostatic hypotension despite adequate treatment.

- Patients with any condition that in the investigator's opinion would make patients unsuitable or interfere with their participation in the study. Potential issues of concern should be raised to the medical monitor during eligibility review.

- Patients who have any clinically significant abnormality or finding from examination, tests, or history that may compromise patient safety.

- Patients who have been treated with an investigational drug within 4 weeks or 5 half-lives (whichever is longer) prior to the beginning of the screening period (this includes investigational formulations of marketed products).

- Prior exposure to CVT-301.

3.5. DETERMINATION OF SAMPLE SIZE

Approximately 350 CVT-301 treatment patients and 175 control patients will be enrolled in this study. It is assumed that the drop-out rate will be approximately 25%.

The primary objective of this study will be to characterize the pulmonary safety within the CVT-301-treated patients and the differences between the groups will be estimated as a secondary objective. However, for the secondary comparison of FEV1 change

between the CVT-301 treatment group and the randomized observational cohort, the standard deviation of FEV1 change from baseline is expected to be 0.281 L, based on data from Study CVT-301-003. Assuming that there is no difference in the changes from baseline between the CVT-301-treated patients and the observational cohort, the study has the following power for the comparison between the 2 groups. The upper limit of the 95% confidence interval for the difference between the 2 groups in change from baseline in FEV1 will be less than 0.121 L with 90% power, assuming 188 and 86 patients completing the study in the CVT-301 treatment group and observational cohort, respectively. The sample size calculation was performed using nQuery Advisor, Version 7.0.

3.6. TREATMENT ASSIGNMENT & BLINDING

This study is a 12-month, open-label, randomized, multicenter study which will evaluate the safety and effects of CVT-301 for the treatment of up to 5 OFF episodes per day in PD patients experiencing motor fluctuations (OFF episodes) and will include a concurrent observational cohort of PD patients managed using the usual standards of care. Patients may have been previously enrolled in the CVT-301-002 or CVT-301-003 studies, or may be CVT-301-naïve. Patients who were previously enrolled in the CVT-301-002 and CVT-301-003 studies will be assigned to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD fine particle dose [FPD]), in this study. Patients who are CVT-301-naïve will be randomized in a 2:1 ratio to the CVT-301 treatment group (CVT-301 at a target nominal respirable dose of 50 mg LD FPD) or the observational cohort. Randomization can occur before the baseline DLCO has been performed. Note: Patients who were enrolled from the CVT-301-002 and CVT-301-003 studies under an earlier version of this protocol (Version 2) were assigned only to the CVT-301 treatment group. Randomization will be stratified by the patient's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each group and by screening spirometry (FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%).

Following completion of SV2 and prior to randomization, the patients' eligibility criteria will be reviewed by delegated staff. Upon confirmation of eligibility, the site will randomize an eligible patient using the Interactive Web Response System (IWRS). The study is an open-label study, so patients and clinical staff will not be blinded to study group assignment.

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.

Since this is an open-label study, 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 not blinded to the inhaled study treatment.

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 reinhaled, T0 is at the end of the reinhalation administration.

During the treatment period, patients will self-administer inhaled study treatment (CVT-301 DL1, 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. For each patient, the planned treatment period will be approximately 52 weeks, and maximum anticipated study duration, including screening and follow-up, will be approximately 62 weeks.

The screening period, which takes place within 35 days prior to Day 1 of the treatment period, will have 2 separate visits: SV1 and SV2 must be separated by at least 4 days. The screening period may be extended an additional 7 days if repeat screening assessments are required.

Before patients return to the clinic for TV/OV1, they will be randomized to treatment. 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 TV/OV1. The subsequent visits during the treatment period take place as follows:

- TV/OV2: Week 4; 28±5 days after TV/OV1.
- TV/OV3: Week 12; 84±14 days after TV/OV1.
- TV/OV4: Week 24; 168±14 days after TV/OV1.
- TV/OV5: Week 36; 252±14 days after TV/OV1.

- TV/OV6: Week 52; 364±14 days after TV/OV1.

Patients who terminate the study early will complete TV/OV6 and return for the Follow-up DLCO visit 4-5 weeks after TV/OV6.

Refer to Protocol Appendices 1 to 15 for tables of study assessments at each visit.

Statistical Analysis Plan

	SV1		SV2		TV/OV1	TV/OV2	TV/OV3	TV/OV4	TV/OV5	TV/OV6
In Clinic Assessments	ON	OFF	ON	OFF	ON*	ON	ON	ON	ON	ON
MMSE	x									
UPDRS Part 1										
UPDRS Part 2					x			x		x
UPDRS Part 3	x	x				x**	x**	x**	x**	x**
UPDRS Part 4					x			x***		x***
C-SSRS					x	x	x	x	x	x
Epworth Sleep Scale					x			x		x
QUIP					x			x		x
PDQ-39					x			x		x
PGI-C								x***		x***
S&E ADL					x			x		x
At home for patients										
PD Diary (only treatment after screening)	x	x	x	x	x	x	x	x	x	x
ON/OFF logs (both groups)	x	x								
Inhaled dosing (CVT-301 only)					x	x	x	x	x	x

* For the CVT 301 arm these assessments are performed pre-dose

** Performed pre-dose, 10, 20, 30, and 60 min post dose (only performed in CVT 301 arm)

*** CVT 301 arm only

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 (TV/OV1) for each variable will be calculated at each subsequent visit.

Percent Predicted = 100 * (Observed) / Predicted, where predicted is calculated and provided to INC by Biomedical Systems (BMS).

4.2. SECONDARY ENDPOINTS

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

- Standard safety endpoints; for definitions see Section 8 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)

- Change from TV/OV1 (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.

- 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.

- Carbon Monoxide Diffusion Capacity (DLCO) assessed over a 12 month period within the CVT 301 treated and the observational ('standard of care') cohorts. Variables will include the absolute DLCO values and DLCO expressed as % of predicted value.

4.3. EXPLORATORY EFFICACY ENDPOINTS

The following endpoints related to the exploratory efficacy objectives will be calculated.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of patients experiencing an OFF episode.

    - The UPDRS Part 3 total score will be calculated as the sum of the individual items of the UPDRS Part 3 questionnaire (UPDRS items 18-31) separately at each time point, i.e. the scores will range from 0 to 108. Missing individual items will be imputed using the 2 non-missing values at time points adjacent to the missing item on the same date. The maximum of the 2 adjacent values will be assigned as the score for the missing item. However, pre-dose values will not be assigned as post-dose values and if one of the adjacent values for a post-dose value is a pre-dose value, only 1 adjacent value will be used. The total score for UPDRS Part 3 assessments will be calculated after imputation of the missing item(s). Missing items at screening will not be imputed. If a pre-dose value is missing, the pre-dose value at the prior visit will be used. A missing TV/OV1 pre-dose value will be imputed using the last screening value in OFF state.

- Time curve of the UPDRS response shown as change from pre-dose in UPDRS Part 3 motor score to 10, 20, 30 and 60 minutes following treatment of patients experiencing an OFF episode in the clinic. The UPDRS Part 3 scores will be derived as described above.

- Change from pre-dose in the average UPDRS Part 3 score at 10 to 60 minutes following treatment of patients experiencing an OFF episode in the clinic. The change from pre-dose to the average of the 4 UPDRS Part 3 total scores (assessments scheduled at 10, 20, 30 and 60 minutes) will be used as the response variable in the statistical analysis.

- A ≥3, ≥6, and ≥11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes following treatment in the clinic (cumulative and non-cumulative). The non-missing UPDRS Part 3 motor scores at each time point (10, 20, 30 and 60 minutes post-dose) are classified as a reduction of ≥3 points or not, reduction of ≥6 points or not and reduction of ≥11 points or not. Furthermore,

for the purpose of the cumulative analysis, the time point (10, 20, 30 and 60 minutes post-dose) when the reduction of ≥3, ≥6 or ≥11 points occurs for the first time will be defined. The categorical scheduled time point is used in this analysis. The missing assessment regarding single items will be managed similarly as describe above. The missing values regarding visits will be managed by considering the missing visits as non-responses.

- 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 having missing data.

- 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, total daily ON time with non-troublesome dyskinesia, and 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 TV/OV1 (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.

- 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 TV/OV1 (baseline) Schwab and England (S&E) Activities of Daily Living (ADL). No further derivation will be done for the S&E scores.

- Change from TV/OV1 (baseline) 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.

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 randomized patients who received at least 1 dose of inhaled CVT-301 and patients from the Observational Cohort who came in for treatment visit 1. Patients will be analyzed according to study treatment 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. Patients will be analyzed according to randomized treatment. The ITT Population will be used for all analyses of exploratory efficacy endpoints.

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.

The deviations will be classified during a review process with the Sponsor and other study personnel (as appropriate) before database lock. The deviations will be classified as minor or major with/without impact on pulmonary assessments during the review process. All decisions regarding major 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 following deviations will be identified, but do not necessarily represent a complete list of potential deviations:

- Administration of PD medications after the usual morning dose of PD medication and before study drug administration
- Incorrect study drug administered at a visit
- Drug non-compliance including but not limited to unapproved dose modification

- Failure to return for defined study visits or within an acceptable visit window for completion of study assessments

The number of subjects with minor, major with/without impact on pulmonary assessments protocol deviations will be summarized by treatment groups and overall. All protocol deviations will be listed.

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 Patient ID (and by visit and by time point, if applicable), unless specified otherwise.

All applicable data will be summarized by treatment group (Observational Cohort or CVT-301) and overall in tables, unless specified otherwise. The CVT-301 group will be broken down into CVT-301-naïve patients and patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies. 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.

For the Observational Cohort, the "start of treatment" will be defined as attendance of TV/OV1, unless specified otherwise. Baseline will be defined as the assessments performed at TV/OV1. In case of missing data, the last non-missing screening assessment will be used as the baseline value.

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 UPDRS and other exploratory 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 the 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.

6.2. KEY DEFINITIONS

Age

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

Age = int ((date of informed consent- 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) =
Date of Screening Visit 1 (M/Y) - Date of diagnosis (M/Y)

Duration of levodopa treatment (months) =
Date of Screening Visit 1 (M/Y) - Start date of levodopa treatment (M/Y)

Time since onset of wearing off episodes (months) =
Date of Screening Visit 1 (M/Y) - Date of onset of wearing off episodes (M/Y)

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

Baseline

For CVT-301 patients, baseline is defined as the last non-missing assessment before the first dose of study drug, unless specified otherwise. For the Observational Cohort, baseline is defined as TV/OV1, or, in the case of missing data, the last non-missing assessment before TV/OV1, unless specified otherwise. However, for all patients who were included in the CVT 301-002 or CVT-301-003 studies, TV/OV1 of the CVT-301-005 study will be used as baseline.

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 and DLCO predicted, adjusted for hemoglobin (Hb)

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 in)*
- *Women predicted DLCO = 2.2382 - (0.1111 x age) + (0.4068 x height in)*

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 observed value is the value provided by TechEd, and the predicted value is the predicted value that provided by BMS and is the values closest to the date of observed value taken. The details are listed in table below.

$DLCO_{predicted}$, percent predicted of FEV1 and FVC	Value selection for Hb, predicted FEV1 and FVC
Screening (prior to randomization)	From TV/OV1 or the value closest to the date of DLCO assessment if the value at TV/OV1 is missing
TV/OV3, within 2 weeks prior to 3	From TV/OV3 or the value closest to the date of DLCO assessment if the value at TV/OV3 is missing
TV/OV4, within 2 weeks prior to 6	From TV/OV4 or the value closest to the date of DLCO assessment if the value at TV/OV4 is missing
TV/OV5, within 2 weeks prior to 9	From TV/OV5 or the value closest to the date of DLCO assessment if the value at TV/OV5 is missing
TV/OV6, within 2 weeks prior to 12	From TV/OV6 or the value closest to the date of DLCO assessment if the value at TV/OV6 is missing
4 to 5 weeks after TV/OV6	The latest non-missing Hb that closest to the date of DLCO assessment taken.

6.3. MISSING DATA

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

- For calculation of the UPDRS part 3 scores, the missing single UPDRS items will be imputed as described in Section 4.3.

- For the primary analysis of spirometry and selected explorative 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 8.1.

- 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 9.1.

- 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 8.4.

The Safety and ITT populations will be used for the analysis of the primary, secondary and exploratory endpoints. 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.

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 Early Termination (ET) visit (PDQ-39, UPDRS Part 2, UPDRS Part 4, S&E ADL score and safety assessments). CVT 301 treated patients will also perform the UPDRS Part 3 assessments at 10, 20, 30, and 60 minutes post dose as well as the PGI-C. The following rules will be used to analyze the data collected at the ET visit:

- For the PDQ-39, PGI-C, UPDRS Part 2, UPDRS Part 3, UPDRS Part 4 and S&E ADL score, the data from the ET visit will be re-assigned to TV/OV6 in case there is no TV/OV6 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 efficacy endpoints (at least the Change from pre-dose in UPDRS Part 3 motor score at 30 minutes post-dose and the mean 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 TV/OV1 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 TV/OV1 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 TV/OV1 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. The percentages will be calculated based on the number of randomized patients, unless otherwise specified). The randomized set will include all randomized patients as well as those from CVT-301-002 and CVT-301-003 studies who were assigned to the CVT 301 treatment group.

- 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 randomized into the 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)
- 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 population by treatment group and overall. 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 TV/OV1 will be used as baseline. If the data are only available on 1 or 2 days prior to TV/OV1, the available data will be used as baseline. If there is no data prior to TV/OV1, 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 TV/OV1 will be used as baseline. If the data are only available on 1 or 2 days prior to TV/OV1, the available data will be used as baseline. If there is no data prior to TV/OV1, 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 TV/OV1)
- Proportion of patients with total daily OFF time <4.5 hours or ≥4.5 hours (from PD diary before TV/OV1)
- 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 TV/OV1, Non-dyskinetic before TV/OV1). 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 TV/OV1 versus non-dyskinetic; Patient with the baseline 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 TV/OV1 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, using the Safety population, will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

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 or TV/OV1 for the observational cohort will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications.

Tables will be generated for the Safety Population. 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. SAFETY

The population used for safety analyses will be the Safety Population. The analyses are outlined below.

8.1. SPIROMETRY

Spirometry will be performed by trained and qualified staff at each study site. 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 DLCO will be summarized descriptively by treatment group and overall.

- Change from baseline to other visits for each parameter. The summary for FEV1 will also be provided by smoker status.
- 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. The screening visit FEV1 data (assessed in ON state) and arrival values at subsequent visits will be used for the calculation.

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 or observational cohort), 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 between CVT-301 and observational cohort at each visit; along with the 95% confidence interval (CI) will be provided in a table. Treatment 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 avisit usubjid;
model chg=base pdsevbl fev1bl trta avisit trta*avisit / ddfm=kr;
repeated avisit / subject=usubjid(trtp) type=un;
lsmeans trtp*avisit / cl;
estimate 'CVT vs OBS Month 1'
        trta 1 -1 trta*avisit 1 0 0 0 0 -1 0 0 0 0 / cl;
estimate 'CVT vs OBS Month 3'
        trta 1 -1 trta*avisit 0 1 0 0 0 0 -1 0 0 0 / cl;
estimate 'CVT vs OBS Month 6'
        trta 1 -1 trta*avisit 0 0 1 0 0 0 0 -1 0 0 / cl;
estimate 'CVT vs OBS Month 9'
        trta 1 -1 trta*avisit 0 0 0 1 0 0 0 0 -1 0 / cl;
estimate 'CVT vs OBS Month 12'
        trta 1 -1 trta*avisit 0 0 0 0 1 0 0 0 0 -1 / cl;
run;
```

The Safety population will be used for the primary analysis.

Sensitivity analyses of the spirometry data

The following sensitivity analysis will be performed for the FEV1, FVC/FEV1 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 arm 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, baseline spirometry value 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 model with treatment group, baseline spirometry value, 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 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 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 TV/OV1 Arrival value. If the TV/OV1 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.

8.2. EXTENT OF EXPOSURE

The following information will be summarized for CVT-301 treated subjects:

- The number of patients with dose change
- Duration of exposure (days)
- Total exposure to study treatment, expressed as person years (sum of exposure to study treatment over all CVT – 301 treated patients)
- 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.

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.

8.3. 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.

8.4. 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 study drug. For the observational cohort, TEAE will be defined as events that occur during/after TV/OV1. 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 overall total. TEAEs with onset after the treatment period are attributed to the treatment group and dose level 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 will be presented (number of TEAEs divided by the total exposure to CVT 301 or observation, 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.

8.5. LABORATORY EVALUATIONS

Laboratory samples for hematology and clinical chemistry will be analyzed by a central

laboratory (located in the United Kingdom for EU sites and the United States for US sites) 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 handling 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.

Statistical Analysis Plan

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 visit 3 assessment. If the visit 3 assessment is missing, the last non-missing screening assessment will be used as baseline. * 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.

8.6. 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 for each parameter. The baseline is defined as the TV/OV1. If TV/OV1 is missing, the last non-missing screening assessment will be used as baseline.
- Actual values and change from pre-dose to post-dose time points at TV/OV1 by time point for each parameter for CVT-301 treated patients
- 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 TV/OV1. 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.

8.7. 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 for each parameter. The baseline is defined as the TV/OV1 value. If TV/OV1 value is missing, the last non-missing screening assessment will be used as baseline.
- 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

8.8. 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

8.9. 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 from baseline table will be constructed to assess any changes in the subjects' suicidal ideation and behavior during the treatment period.

8.10. 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 will be summarized by treatment group and overall (for handling of data from the ET visit, see Section 6.4).

8.11. 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.

The frequency and percentage of patients with positive response for each of the item within each section will be summarized by visit 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

8.12. UPDRS PART 4

Changes from baseline to the subsequent visits in UPDRS Part 4 sum scores (dyskinesia sum score, wearing-off sum score) will be analyzed using a similar MMRM as for the UPDRS Part 3 scores (described below) to estimate the within-group changes. Otherwise, the data will be presented with descriptive statistics only classified by visit for CVT treated patients. The observed cases will be used in the analysis and summaries.

8.13. 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. EXPLORATORY EFFICACY

9.1. EXPLORATORY EFFICACY ENDPOINT AND ANALYSIS

The ITT population will be used for the exploratory efficacy analysis. Patients will be analyzed according to randomized treatment. The within group changes from baseline in continuous efficacy variables will be estimated using an MMRM. No between group differences will be calculated, unless otherwise specified. The model will include visit and the stratification variables (Hoehn and Yahr stage and screening FEV1 and/or FEV1/FVC) as fixed factors. The baseline value will be used as a covariate. For variables which do not have a pretreatment baseline assessment, OFF-state baseline UPDRS Part 3 score will be used as the baseline covariate. An unstructured covariance structure will be applied for the MMRM. In case the model will not converge with the unstructured covariance structure, compound symmetry will be used instead. For all patients, categorical data will be evaluated descriptively. Each visit will be evaluated separately for the categorical endpoints. The exploratory efficacy endpoints and associated analyses are as follows. For the detailed definition of the endpoints, see Section 4.3.

- Change from pre-dose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes and the average of the motor score at 10-60 following treatment of patients experiencing an OFF episode in the clinic. Change from pre-dose in the average UPDRS Part 3 score at 10 to 60 minutes is calculated as the mean of change of UPDRS Part III total score from pre-dose to each time point post-dose if UPDRS Part III total score is available for at least 2 time points post-dose. The scheduled post-dose UPDRS Part III assessments are at 10, 20, 30, 60 minutes post-dose, respectively. If there is more than 2 time points post-dose with missing UPDRS Part III total score, the change of UPDRS Part III total score from pre-dose to 10 to 60 minutes post-dose will be missing. A MMRM model as defined above will be used.

- Time curve of the UPDRS response shown as change from pre-dose in UPDRS Part 3 motor score to 10, 20, 30 and 60 minutes following treatment of patients experiencing an OFF episode in the clinic. A separate MMRM model will be fitted for each of the time points.

- A ≥3, ≥6, and ≥11 point reduction in the UPDRS Part 3 motor score from pre-dose to post-dose, at 10 to 60 minutes following treatment in the clinic (cumulative and non-cumulative). For the non-cumulative analysis, the proportions of patients with a reduction will be tabulated by treatment group, visit and time point. For the cumulative analysis, the cumulative proportions of patients who achieved the first reduction before or at the time point in question will be tabulated by visit and time point.

- 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.

- 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. However, the baseline daily OFF time will be used as a covariate in the MMRM model instead of the OFF-state baseline UPDRS part 3 score. 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.

- 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.

- Changes from TV/OV1 in endpoints based on S&E ADL score, UPDRS Part 2 score, and PDQ-39 sub-scores. An ANCOVA model with the treatment group and stratification variables as fixed factors and the TV/OV1 value as a covariate will be used to estimate the treatment differences. Otherwise, the data will be presented with descriptive statistics only classified by treatment group and visit. The observed cases will be used in the analysis and summaries.

Sensitivity analyses of the exploratory efficacy data

The following sensitivity analysis will be performed for the UPDRS Part 3 motor scores at 30 minutes post-dose and daily OFF time exploratory efficacy endpoints.

- 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 arm 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 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 spirometry value, 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.

10. INTERIM ANALYSES

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

Data summary, which will not affect study conduct, may be prepared to support regulatory submission.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes from the analyses planned in the protocol.

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:

- 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 treatments in the tables will be Placebo first, followed by CVT-301 and a total 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
Minimum	XXX,
Maximum	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. 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.

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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Not Applicable.

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

Acorda Therapeutics, Inc., CVT-301 Type B Pre-NDA FDA Meeting Minutes dated 27 October 2016.

FDA Guidance for Industry: Assessment of Abuse Potential of Drugs January 2017.

Setnik, B. A consensus list proposal for adverse events related to abuse and dependence potential, February 16, 2016, International society for CNS clinical trials and methodology (ISCTM) 12th Annual Scientific Meeting, The Fairmont, Washington, DC, February 16, 2016.

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