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RESEARCH**

APPLICATION NUMBER:

209184Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Susanne R. Goldstein, MD
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Established Name	CVT-301 levodopa inhalation powder
(Proposed) Trade Name	Inbrija
Therapeutic Class	
Applicant	Acorda Therapeutics, Inc.

Formulation(s)	Capsule
Dosing Regimen	inhaled
Indication(s)	OFF periods in Parkinson's disease
Intended Population(s)	Patients with idiopathic Parkinson's disease

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment.....	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	9
1.4	Recommendations for Postmarket Requirements and Commitments	10
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	10
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	14
3	ETHICS AND GOOD CLINICAL PRACTICES.....	14
3.1	Submission Quality and Integrity	14
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures.....	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1	Chemistry Manufacturing and Controls	16
4.2	Clinical Microbiology.....	Error! Bookmark not defined.
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action.....	
4.4.2	Pharmacodynamics.....	
4.4.3	Pharmacokinetics.....	Error! Bookmark not defined.
5	SOURCES OF CLINICAL DATA.....	26
5.1	Tables of Studies/Clinical Trials	26
5.2	Review Strategy	31
5.3	Discussion of Individual Studies/Clinical Trials.....	
6	REVIEW OF EFFICACY	31
	Efficacy Summary.....	31
6.1	Indication	32
6.1.1	Methods	32
6.1.2	Demographics.....	35
6.1.3	Subject Disposition	37
6.1.4	Analysis of Primary Endpoint(s)	38
6.1.5	Analysis of Secondary Endpoints(s).....	Error! Bookmark not defined.

6.1.6	Other Endpoints	
6.1.7	Subpopulations	45
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	Error! Bookmark not defined.
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	46
6.1.10	Additional Efficacy Issues/Analyses	
7	REVIEW OF SAFETY	60
	Safety Summary	60
7.1	Methods.....	60
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	60
7.1.2	Categorization of Adverse Events.....	
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	
7.2	Adequacy of Safety Assessments	62
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	62
7.2.2	Explorations for Dose Response.....	63
7.2.3	Special Animal and/or In Vitro Testing	
7.2.4	Routine Clinical Testing	
7.2.5	Metabolic, Clearance, and Interaction Workup	
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	
7.3	Major Safety Results	65
7.3.1	Deaths.....	66
7.3.2	Nonfatal Serious Adverse Events	67
7.3.3	Dropouts and/or Discontinuations	77
7.3.4	Significant Adverse Events	Error! Bookmark not defined.
7.3.5	Submission Specific Primary Safety Concerns	82
7.4	Supportive Safety Results	88
7.4.1	Common Adverse Events	88
7.4.2	Laboratory Findings	91
7.4.3	Vital Signs.....	91
7.4.4	Electrocardiograms (ECGs)	94
7.4.5	Special Safety Studies/Clinical Trials.....	Error! Bookmark not defined.
7.4.6	Immunogenicity	Error! Bookmark not defined.
7.5	Other Safety Explorations.....	Error! Bookmark not defined.
7.5.1	Dose Dependency for Adverse Events	Error! Bookmark not defined.
7.5.2	Time Dependency for Adverse Events.....	Error! Bookmark not defined.
7.5.3	Drug-Demographic Interactions	Error! Bookmark not defined.
7.5.4	Drug-Disease Interactions.....	Error! Bookmark not defined.
7.5.5	Drug-Drug Interactions.....	Error! Bookmark not defined.
7.6	Additional Safety Evaluations	Error! Bookmark not defined.
7.6.1	Human Carcinogenicity.....	Error! Bookmark not defined.
7.6.2	Human Reproduction and Pregnancy Data..	Error! Bookmark not defined.

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	95
7.7	Additional Submissions / Safety Issues.....	Error! Bookmark not defined.
8	POSTMARKET EXPERIENCE.....	98
9	APPENDICES	99
9.1	Literature Review/References	Error! Bookmark not defined.
9.2	Labeling Recommendations	99
9.3	Advisory Committee Meeting.....	Error! Bookmark not defined.

Table of Tables

APPEARS THIS WAY ON ORIGINAL

Table of Figures

APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of CVT-301 (Inbrija) 84mg (two 42mg capsules) oral inhalation for the treatment of OFF periods in patients with Parkinson's disease as an adjunct to a carbidopa levodopa regimen up to 5 times per day, as needed. The maximum dose of CVT-301 in humans should not exceed 420 mg inhaled levodopa/day.

1.2 Risk Benefit Assessment

The efficacy results for the treatment of OFF periods in patients with Parkinson's disease as an adjunct to carbidopa levodopa regimen in the pivotal study, **CVT-301-004** is statistically significant for the primary endpoint, the change in UPDRS part 3 score at 30 minutes post dose at Week 12, at 84mg (Dose Level 2) inhalation.

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.92
95% confidence interval	(-6.84, -1.00)
P-value	0.009

The key secondary endpoint, the proportion of patients achieving resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment, was also statistically significant at 84mg (Dose Level 2).

Statistics	Placebo vs CVT-301 84mg
Common odds ratio (odds in CVT-301 84mg / odds in placebo)	2.4
95% confidence interval	(1.35, 4.26)
P-value	0.003

Results from four Phase 3 studies, two placebo-controlled and 2 long-term follow-up studies were submitted to evaluate safety of CVT-301 for the treatment of OFF episodes in patients with PD. In Study CVT-301-004, patients were randomized to either DL1 (60mg), DL2 (84mg) or placebo for a 12-week maintenance period, provides the most interpretable information for adverse events at the to-be-marketed dose of 84mg.

The overall exposure, including long term exposure met the regulatory requirements for approval.

The most common treatment emergent adverse was cough, which most likely due to the route of administration, inhalation

. The other adverse events are similar to those described in the label for the listed drug Sinemet oral tablets.

Study CVT-301-004 All Adverse Reaction 2% or Higher in Any CVT 301 Group and Greater than Placebo

System Organ Class	Preferred Term	CVT 301 60 mg N=113 %	CVT 301 84 mg N=114 %	Placebo N=112 %
Respiratory, thoracic and mediastinal	Cough	15	15	2
Infections and infestations	Upper respiratory tract infection	2	6	3
Gastrointestinal disorders	Nausea	0	5	3
Respiratory, thoracic and mediastinal	Sputum discolored	0	5	0
Nervous system disorders	Dyskinesia	4	4	0
Gastrointestinal disorders	Vomiting	0	3	0
Infections and infestations	Nasopharyngitis	2	3	2
Injury, poisoning and procedural complications	Fall	4	3	2
General disorders and administration site	Chest discomfort	0	2	0
Injury, poisoning and procedural complications	Laceration	2	2	0

The applicant conducted pulmonary function testing in the double placebo-controlled trials (CVT-30-003, CVT-301-004), open label extension trial (CVT-301-004E) as well as a dedicated open label pulmonary safety study (CVT-301-005). The information from these trials was reviewed in consultation with the Division of Pulmonary, Allergy and Rheumatologic Products (DPARP). It was concluded that there was no safety signal in pulmonary function testing that would preclude the approval of Inbrija.

The clinical trials results and information in the Applicant's submission demonstrates that CVT-301 84mg (two 42mg capsules) is effective for the treatment of OFF episodes in patients with Parkinson's disease on a carbidopa levodopa regimen. The review of the safety information in this submission reveals that CVT-301 can be used safely for the treatment of OFF episodes in patients with Parkinson's disease as an adjunct to carbidopa levodopa regimen at the recommended dose of 84mg (two 42mg capsules) oral inhalation up to 5 times per day, as needed. The maximum dose of CVT-301 in humans should not exceed 420 mg inhaled levodopa/day.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This application does not require a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

This application does not require PMR or PMC.

2 Introduction and Regulatory Background

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Acorda Therapeutics is relying on the Agency's finding of safety as well as labeling for the reference listed drug (RLD) Sinemet oral tablets (NDA 017555, approved on MAY 2, 1975).

2.1 Product Information

CVT-301 is a dry powder formulation of levodopa (LD) for inhalation and represents a novel drug and device combination product. The combination of particle size and formulation composition has been designed to provide therapeutic levels of LD following inhalation and rapid absorption into the pulmonary circulation.

CVT-301 is delivered to the lung using a capsule-based, breath-actuated inhaler, the CVT-301 inhaler.

2.2 Tables of Currently Available Treatments for Proposed Indications

Apomorphine (Apokyn) subcutaneous

2.3 Availability of Proposed Active Ingredient in the United States

Active ingredient levodopa is available in combination with carbidopa in the following products:

Drug	Preparation
Systemic	
Sinemet	Oral
Sinemet CR	Oral
Stalevo	Oral
Rytary	Oral
Duopa	Enteral suspension

2.4 Important Safety Issues with Consideration to Related Drugs

As with other dopaminergic drug products, important safety concerns include:

- Impulse control disorder
- Hallucinations/psychosis
- Dopamine Dysregulation Syndrome
- Orthostatic hypotension
- Dyskinesia

Due to the route of delivery, pulmonary safety issues (shortness of breath, cough, respiratory infections, and decrease in respiratory function) are also of concern.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- **pre-IND meeting** held November 27, 2012
 - o NDA could be filed as 505(b)(2)
- **Type B EOP2 meeting** July 10, 2014
 - o Bridge to Sinemet
 - o Pivotal Phase 3 study, CVT-301-004, and supportive efficacy study CVT-301-003
- **Type C Meeting** February 22, 2016 (WRO)
 - o Long term open-label studies CVT-301-004E and CVT-301-005
- **Type B pre-NDA Meeting** August 25, 2016
 - o Integrated Summary of Efficacy not necessary; only one pivotal and one additional efficacy study
 - o Safety database, including 120-day safety update
- **NDA submitted** June 27, 2017
- **RTF** August 25, 2017 re: HFE studies
- **NDA resubmission** December 5, 2017
- **120 Day Safety update** March 16, 2018
 - o Cutoff date December 20, 2017

Acorda Therapeutics, Inc. (Acorda) has developed CVT-301 (levodopa inhalation powder) as needed for intermittent treatment of symptoms of OFF periods in patients with PD as an adjunct to a carbidopa/ levodopa regimen. Acorda acquired the investigational product and IND 115750 on 22 October 2014 from the original development company: Civitas Therapeutics, Inc. (Civitas), now a wholly owned subsidiary of Acorda.

Acorda submitted an original 505(b)(2) NDA on June 27, 2017. On August 25, 2017, the applicant received an FDA Refusal to File (RTF) Letter because of Chemistry, Manufacturing and Controls (CMC) deficiencies.

Refusal to File Reasons

Chemistry, Manufacturing and Controls

1. As stated in your August 3, 2017, amendment, the Acorda Therapeutics, Inc., Chelsea, MA manufacturing site (FEI number 3011696115) is not ready for inspection, and will not be ready until September 1, 2017.

2. The NDA does not contain the proposed or actual master production record for the drug component (levodopa capsules). Submission of this information is required under 314.54(a)(1)(i).

Office of Medication Error Prevention and Risk Management

We refer to IND 115750 and your human factors (HF) validation protocol submitted to the Agency on July 13, 2016, and our Agency comments dated October 19, 2016. We also refer to your current June 27, 2017, submission of HF validation study results. Our preliminary review of your HF validation protocol and results identified the following deficiencies in your study methodology:

Your protocol submitted on July 13, 2016, stated that all patient participants will be trained. In our October 19, 2016, comments, we informed you that we find these scenarios not reflective of real use without justification of how training all patient participants is reflective of real use. We acknowledge your response to justify the use of an all trained patient user group is supported by a training survey where respondents stated they believe they will receive training. However, you did not submit this justification for Agency concurrence prior to commencing your study. Your survey results did not confirm that every patient user will consistently receive training. As such, you should include data from 15 untrained patients and 15 untrained caregivers.

Your protocol submitted on July 13, 2016, states you will include a mixture of age, ethnicities, and education levels. In our October 19, 2016, comments to you, we communicated that it is unclear whether this approach is appropriate to ensure each user group is representative of the intended user population and we asked you to provide a justification for this strategy. However, 14 of the 15 participants presented in your June 27, 2017, submission are college educated. We do not believe that all intended users will have college degrees. You should provide data from users who have mixture of education levels, include those with less than college education level.

Office of Scientific Investigation

Please provide contact information for all clinical sites for Protocol CVT-301-004 including telephone number, fax number, and email address for the clinical investigator.

For Protocol CVT-301-004, two CROs are listed as responsible for clinical site monitoring: [REDACTED] (b) (4). Please describe the specific monitoring functions performed by both of these CROs.

Please correct the bookmarks for the document BIMO-CVT-301-004-line-listing included in the submission. The bookmarks are correct up to Site #5045.

Controlled Substance Staff

Some of the data are not easily accessed:

Not all links for studies (non-clinical and clinical) and references related to the assessment of abuse potential are functional.

In many instances, links are not provided to the specific sections in the application addressing data of interest. For example, a link is provided to the whole ISS or study report, instead of directing the reviewer to a particular table or section. To facilitate the review of the application you should provide specific links to the topics discussed.

Under IND 115750 and throughout the development of this novel formulation, CSS provided detailed requests for the evaluation of dependence, withdrawal, and rebound to be implemented in the still on-going study # CVT-301-004E. However, you indicate, in the study report # CVT-301-004E, that only 7 out of 69 sites implemented these changes. Additionally, no data were submitted in the current NDA, as you apparently plan to submit these data at the 120-day update. If the application is resubmitted, this information should be provided at the time of resubmission. The acceptability of those data to address the evaluation of dependence, withdrawal, and rebound will be a review issue.

Provide information on overdoses, both intentional and unintentional. There is a link to the ISS in the abuse potential report, but no data on overdose were found in the ISS. Provide the summary of overdoses for all subjects who used 8 or more doses on any given day in all studies with links to CRFs included. The information on overdoses cannot be located in the ISS, nor can they be found in the study reports # CVT-301-004, CVT-301-004E, and CVT-301-005.

Provide drug accountability data for the entire clinical development program, along with discrepancies in the amount of the clinical supplies of the study drug dispensed and the amount of drug lost or otherwise not accounted for, and the reason for missing drug if known.

Resubmission

The applicant addressed the two CMC issues as well as the 9 other non-filing issues described in the RTF Letter and **resubmitted** the 505(b)(2) New Drug Application (NDA) for CVT-301 (levodopa inhalation powder) on **December 5, 2017**.

Discipline Review Letter

On May 7, 2018, the applicant was sent a Discipline Review Letter. The Division identified deficiencies in the applicant's human factors (HF) validation study submitted on December 5, 2017:

The applicant's HF validation study methodology was flawed; thus, the results are ultimately not generalizable to the intended user population. The study did not include a representative group of untrained patient users. For the "untrained" patient participants, the study moderator provided the following instruction:

To address this deficiency, you should perform a supplemental HF validation study using appropriate methodology with 15 representative untrained patient participants. We recommend that you submit a new HF study protocol for the Agency's review and feedback prior to commencing your HF validation study. In addition, we provide recommendations for your instructions for use and container label below to promote the safe use of your product and recommend they are implemented prior to initiating your HF validation study.

Instructions for Use (IFU)

The instruction regarding cleaning the inhaler appears to include conflicting information. The sentences "You do not need to clean the inhaler. You can use a dry cotton swab or tissue to wipe the outside of the inhaler" should be clarified to specify which parts of the inhaler (e.g. inside of the inhaler, outside of the inhaler) should or should not be cleaned.

Container label (blister)

The container label (blister) should be revised to include the phrase "For oral inhalation only" on the principal display panel (PDP). We recommend this revision to mitigate the risk of incorrect route of administration errors.

In a separate information request, sent July 5, 2018, reviewers from the Center for Devices and Radiological health (CDER) notified the Applicant of deficiencies in the device testing for leachables and extractables testing and testing for the device output airs.

In response to the Discipline Review Letter, the applicant submitted additional material on September 5 and 10, 2018, which constituted a **major amendment** to the application. Therefore, the PDUFA goal date was extended to January 5, 2019.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the review cycle for the current submission (12.5/2017), there were 13 Information Requests (IR) from the Quality Assessment Team, for which the applicant submitted responses. The IRs are outlined in the table below.

Submissions Reviewed	Document Date	Disciplines Affected
SD-10, Response to IR	03/01/2018	Product, CDRH
SD-13, Response to IR	04/05/2018	Product
SD-15, Response to IR	04/30/2018	Biopharmaceutics
SD-16, Labeling/Container	05/25/2018	Labeling
SD-18, Response to IR	06/29/2018	Product
SD-19, Response to IR	07/05/2018	CDRH
SD-20, Labeling/Container	07/09/2018	Labeling
SD-21, Response to IR	08/03/2018	Process
SD-24, Response to IR	08/21/2018	Process
SD-26, Response to IR	09/05/2018	CDRH
SD-27, Response to IR	09/09/2018	CDRH
SD-28, Response to IR	09/10/2018	CDRH
SD-28, Response to IR	09/14/2018	CDRH

3.2 Compliance with Good Clinical Practices

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the ICH Consolidated Guideline on Good Clinical Practice.

The electronic data capture (EDC) was conducted in adherence to the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials. In addition, this study adhered to all local regulatory requirements. Acorda Therapeutics included a Debarment Certificate (module 1.3.3) stating that:

Acorda Therapeutics, Inc., certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this 505(b)(2) NDA 209184 submission for CVT-301 (levodopa inhalation powder.)

3.3 Financial Disclosures

The applicant submitted Certification: Financial Interests and Arrangements of Clinical Investigators: Form FDA 3454, signed by Dr. Burkhard Blank, April 24, 2017 (module 1.3.4.). The Applicant provided the information required for investigators with disclosable financial relationships and a list of investigators without a disclosable financial relationship with the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

DRUG PRODUCT and DEVICE

CVT-301 (levodopa inhalation powder) is delivered by oral inhalation using a proprietary delivery system: a capsule-based, breath-actuated inhaler. The inhaler is approximately 5 inches long and consists of a blue cap, blue handle, and white mouthpiece covering the capsule chamber. For clinical administration, the capsule is placed into the inhaler, punctured during a simple actuation process, and the contents of the capsule are inhaled through the mouthpiece.

The proposed drug/device combination product comprises hypromellose (HPMC) capsules containing a spray-dried formulation of levodopa (42 mg), 1,2-dipalmitoyl-*SN*-glycero-3-phosphocholine (DPPC), and sodium chloride, to be administered using a co-packaged proprietary breath-actuated inhaler.

The general outer appearance of the inhaler is provided in Figure 1, Figure 2, Figure 3,. A schematic diagram showing all components is provided in Figure 4.

(b) (4)



Figure 4: Schematic Diagram of CVT-301 Inhaler Components



Source: Applicant

The inhaler components are listed in Table 1 below. There are no accessories for the inhaler.

Table 1: Composition of CVT-301 (Levodopa Inhalation Powder) Capsules, (b) (4) 42 mg

Ingredient	Function	Quality Standard	Quantity per Capsule	
			(b) (4)	42 mg-LD (% wt)
Levodopa	Active	USP/EP		(b) (4)
DPPC				(b) (4)
NaCl				
Formulation Total			(b) (4)	
				(b) (4)

DPPC = 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; HPMC = hypromellose or hydroxypropyl methylcellulose (b) (4)

Source: Applicant

The proposed commercial configuration is a carton containing 92 blister packaged capsules and one inhaler. To administer a dose of 84mg (two 42mg capsules), the patient removes the outer cap and mouthpiece, then places one capsule in body of the device. When the mouthpiece is reattached, the device punctures the capsule and is ready for use. The patient is instructed to: 1) breathe out; 2) place the mouthpiece into their mouth; 3) breathe in deeply until they hear and feel the capsule spinning; 4) take the inhaler out of their mouth; 5) hold their breath for 5 seconds and then exhale. The first capsule is

removed from the device and a second capsule is administered in the same manner. The inhaler should be discarded after all capsules have been administered.

The OPQ team review focused on evaluation of submitted manufacturing and control information to support the quality of the drug component and its compatibility with the device, and on the adequacy of the controls for the finished combination product to ensure the safety and efficacy of the dose delivered to the patient (DARRTS 12/14/2018). The Center for Devices and Radiological Health (CDRH) evaluated the design, safety/biocompatibility, and performance of the device component (DARRTS 12/14/2018.)

Device performance (reviewed by OPQ) and supporting data for device robustness (reviewed by CDRH) were deemed adequate. The CDRH team identified deficiencies related to biocompatibility of direct and indirect patient contact surfaces. These deficiencies, which were related to inadequate testing for extractables/leachables, volatile organic compounds, and fine particles were communicated to the sponsor in an interactive review request (6/27/2018). The applicant provided the requested information during the interactive review. Based on the data from additional testing performed by the applicant during the review cycle, CDRH recommended approval from a device perspective

4.3 Preclinical Pharmacology/Toxicology

No excipients, impurities or leachables/extractables were found to be toxicologically relevant and inhalation studies of the excipient DPPC at greater than clinically anticipated levels, resulted in no differences from controls in either rat or dog.

In a safety pharmacology study, single doses of inhaled air or CVT-301 (7.5 mg/kg) caused no abnormalities in respiratory or cardiovascular function in Beagle dogs.

In a comparison study in rats, the C_{max} after drug inhalation was less than that seen after IV bolus, but greater than that seen after oral administration.

Inhaled CVT-301 was administered in toxicity studies of 7 and 28 days to rat and dog and 6 months to rat; in all studies the NOAEL was at the achieved HD, which ranged from 912 mg/m² (28-day dog) to 1008 mg/m² (56-day rat). Studies in rat (nose-only inhalation) and dog (oro-nasal face mask) showed effects from the delivery devices; histologic changes were nonspecific responses to the presence of the particulates in the nasal cavity (rat) and lungs (dog). No systemic toxicity was observed.

The no adverse effect level doses in rat and dog exceed the recommended maximal human dose by three and one half to four-fold.

4.4 Clinical Pharmacology

CVT-301 Drug and Device Combination Product

CVT-301 is a drug and device combination product (powder-filled capsules for oral inhalation and breath-actuated inhaler device) designed to deliver levodopa (LD) powder, in a new formulation and delivery system by a new pulmonary route of delivery. The proposed use of CVT-301 represents a new indication for LD as an adjunct for treatment of OFF periods in PD patients on a CD/LD regimen.

CVT-301 is intended for oral inhalation for use in adult PD patients (18+ years) and was studied in the Phase 3 program at a dose of **two** 30 mg or **two** 42 mg levodopa capsules that provided 60 mg or 84 mg levodopa, and delivered 35 mg or 50 mg levodopa fine particle dose (FDP) to the lungs, respectively. The intended to-be-marketed dose is 84 mg levodopa (two 42 mg capsules) with a maximum recommended use in the proposed label of up to 5 times per day, as needed. The maximum dose of CVT-301 in humans should not exceed 420 mg levodopa/day.

The to-be-marketed commercial formulation of CVT-301 (levodopa inhalation powder) is a spray-dried dry powder formulation composed of (b) (4) levodopa, and excipients (b) (4)

The pharmacokinetic (PK) development program included 3 Phase 1 studies, CVT-301-001, CVT-301-006, and CVT-301-010, conducted in healthy volunteers, and 2 Phase 1 studies in special populations, Study CVT-301-007 (in smokers and non-smokers) and Study CVT-301-008 (in asthmatics.)

Table 2 Overview CVT-301 Clinical Pharmacology Studies

Study Identifier (Location in this Module)	Study Phase	Clinical Pharmacology Objectives	Study Design	Study Population	Study Treatment ^a
CVT-301-001 (Section 2.1)	Phase 1	To evaluate the fasted PK of single ascending doses of CVT-301; To compare fasted PK of CVT-301 to oral LD administered in the fasted and fed state; To compare the fasted PK of CVT-301 with or without pretreatment with CD.	Open-label, non-randomized, 2-part cross-over study: Part A (dose escalation segment); Part B (± CD pretreatment segment)	Healthy volunteers	Part A: 10, 20, 30, 50 mg LD FDP; Lodosyn® (CD) 25 mg; Co-Careldopa® (CD/LD) Tablets 25 mg/100 mg Part B: 40 mg LD FDP; Lodosyn (CD) 50 mg

CVT-301-006 (Section 2.2)	Phase 1	To investigate the fasted PK of higher doses of CVT-301; To characterize the PK of LD metabolites following a single inhaled dose of CVT-301 and a single oral Sinemet 25/100 administration; To explore the dose proportionality of LD following single inhaled dose administration and a single fasted oral Sinemet 25/100 administration.	Non-randomized, open-label, 5-period study	Healthy volunteers	50 mg low-fill capsule, 70 mg, 105 mg, 50 mg high-fill capsule weight LD FPD; Sinemet 25/100 tablets; Lodosyn (CD) 50 mg
CVT-301-010 ^b (Section 2.3)	Phase 1	To determine the fasted relative bioavailability of 2 CVT-301 30 mg and 42 mg capsules compared with Sinemet, the reference product for the 505(b)(2) NDA. To determine fasted dose proportionality of 2 CVT-301 30 mg capsules and 2 CVT-301 42 mg capsules.	Open-label, randomized, 3-period cross-over single dose PK bridging study to compare 2 doses of CVT-301 with an oral dose of Sinemet (carbidopa-LD) tablets	Healthy volunteers	60 mg and 84 mg LD; Sinemet 25/100 Using to-be-marketed commercial product.

Abbreviations: FPD = fine particle dose; PK = pharmacokinetics; LD = levodopa; CD = carbidopa

Note: In studies using a placebo, the placebo capsule consisted of inhalation grade, non-respirable lactose that generally does not enter the lungs upon inhalation due to the molecule size. See individual study summaries for CD pretreatment schedule and dosing in the fed and fasted states

^a LD FPD is the estimated LD dose delivered to the lower lung.

^b CVT-301-010 is the definitive relative bioavailability study bridge to Sinemet; it used the same fill weight and formulation of CVT-301 as was used in the pivotal Phase 3 study CVT-301-004.

Source: Applicant

In addition, PK data was collected in Study CVT-301-002, a Phase 2a study, conducted in patients with PD that utilized a different than to be marketed CVT-301 inhaler.

No PK data was collected during the supportive Phase 2b or the pivotal Phase 3 studies. However, the **to-be-marketed formulation's** PK was characterized in healthy subjects in a Phase 1 CVT-301-010 study.

Study CVT-301-010

Title of the Study: A Phase I Single Dose Pharmacokinetic Bridging Study to Compare Two Dose Strengths of CVT-301 (Levodopa Inhalation Powder) With an Oral Dose of SINEMET® (Carbidopa-Levodopa) Tablets.

Primary Objective

- To determine the relative bioavailability of CVT-301 to-be-marketed 30 mg and 42 mg capsules compared with the reference product on a per milligram basis

Secondary Objectives

- To determine the unadjusted relative bioavailability of 2 CVT-301 30 mg and 42 mg capsules compared with the reference product
- To determine dose proportionality of 2 CVT-301 30 mg capsules and 2 CVT-301 42 mg capsules on a per milligram basis
- To assess the single-dose safety and tolerability of CVT-301 compared to Sinemet

Results

PK parameters of LD unadjusted and adjusted for Baseline are presented in Tables 3 and 4.

Table 3 Study CVT-301-010: Summary of Pharmacokinetic Parameters for LD – Unadjusted for Baseline

Parameter	Treatment		
	Sinemet 25/100 (N=24)	60 mg CVT-301 (N=24)	84 mg CVT-301 (N=24)
AUC _{0-4h} (h•ng/mL)	2430 (28.8)	1000 (24.9)	1320 (32.9)
DN-AUC _{0-4h} (h•ng/mL/mg)	24.3 (28.8)	16.7 (24.9)	15.8 (32.9)
AUC _{0-24h} (h•ng/mL)	3080 (29.0)	1300 (27.2) ^b	1790 (31.8) ^b
DN-AUC _{0-24h} (h•ng/mL/mg)	30.8 (29.0)	21.7 (27.2) ^b	21.4 (31.8) ^b
C _{max} (ng/mL)	1640 (35.7)	532 (29.2)	708 (33.9)
DN-C _{max} (ng/mL/mg)	16.4 (35.7)	8.86 (29.2)	8.43 (33.9)
C _{10min} (ng/mL)	89.9 (158.1)	352 (43.2)	434 (54.4)
C _{min} (ng/mL)	23.7 (50.8) ^b	20.4 (48.2)	24.8 (40.4)
T _{max} ^a (minute)	45 (19-122)	30 (10-120)	30 (10-120)
T _½ (h)	2.16 (52.0) ^b	2.16 (53.1) ^b	2.38 (72.0) ^b
Vz/F (L)	124 (87.2) ^b	172 (64.6) ^b	172 (66.0) ^b

Note: Geometric mean (CV%) data are presented unless otherwise noted.

Abbreviations: AUC = area under plasma concentration-time curve; C_{10min} = plasma concentration at 10 minutes postdose; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CV = coefficient of variation; DN = dose normalized; N = number of subjects; T_½ = apparent terminal elimination half-life;

T_{max} = time to maximum plasma concentration; Vz/F = apparent terminal volume of distribution. ^a Median (range).

^b N < 24.

See [Section 2.3.2](#) for pretreatment and concurrent CD dosing information.

Table 4 Study CVT-301-010: Summary of Pharmacokinetic Parameters for LD – Adjusted for Baseline

Parameter	Treatment		
	Sinemet 25/100 Oral Dose (N=24)	60 mg CVT-301 (N=24)	84 mg CVT-301 (N=24)
AUC _{0-4h} (h•ng/mL)	2390 (28.9)	965 (23.6)	1280 (34.3)
DN-AUC _{0-4h} (h•ng/mL/mg)	23.9 (28.9)	16.1 (23.6)	15.2 (34.3)
AUC _{0-24h} (h•ng/mL)	2880 (29.2)	1170 (23.2) ^b	1630 (30.1) ^b
DN-AUC _{0-24h} (h•ng/mL/mg)	28.8 (29.2)	19.6 (23.2) ^b	19.4 (30.1) ^b
C _{max} (ng/mL)	1630 (35.9)	522 (28.9)	696 (35.1)
DN-C _{max} (ng/mL/mg)	16.3 (35.9)	8.70 (28.9)	8.28 (35.1)
C _{10min} (ng/mL)	64.6 (333.9)	342 (42.7)	418 (59.2)
C _{min} (ng/mL)	9.61 (196.8) ^b	9.86 (95.5)	8.98 (126.4)
T _{max} ^a (minute)	45 (19-122)	30 (10-120)	30 (10-120)
T _{1/2} (h) ^b	1.88 (49.6)	1.96 (75.7)	2.30 (40.4)
Vz/F (L) ^b	96.2 (54.4)	144 (73.2)	168 (49.2)

Note: Geometric mean (CV%) data are presented unless otherwise noted.

Abbreviations: AUC = area under plasma concentration-time curve; C_{10min} = plasma concentration at 10 minutes postdose; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CV = coefficient of variation; DN = dose normalized; N = number of subjects; T_{1/2} = apparent terminal elimination half-life;

T_{max} = time to maximum plasma concentration; Vz/F = apparent terminal volume of distribution. ^a Median (range).

^b N < 24

See Section 2.3.2 for pretreatment and concurrent CD dosing information.

Source: Study CVT-301-010 CSR Table 8.

Source: Applicant

Statistical analyses of baseline-unadjusted dose-normalized AUC_{0-24h} and dose-normalized C_{max} to assess the relative bioavailability of LD following oral dose of carbidopa levodopa 25/100 and inhaled doses of CVT-301 60mg and CVT-301 84mg are presented in Table 5.

Table 5 Study CVT-301-010: Dose-Normalized AUC_{0-24h} and C_{max} for LD following Oral Doses of Sinemet 25/100 and Inhaled Doses of 60 mg and 84 mg CVT-301 - Unadjusted for Baseline

Dose-Normalized PK Parameter	Dose Level	Geometric LS Means	Ratio (%) CVT-301/Sinemet	90% CI of the Ratio	
				Lower (%)	Upper (%)
DN-C _{max} (ng/mL/mg)	Sinemet 25/100	16.4 ^a			
	60 mg CVT-301	8.9 ^a	53.9	47.1	61.8

	84 mg CVT-301	8.4 ^a	51.3	44.8	58.7
DN-AUC _{0-24h} (h•ng/mL/mg)	Sinemet 25/100	30.8 ^a			
	60 mg CVT-301	21.8 ^b	70.8	64.6	77.6
	84 mg CVT-301	21.3 ^b	69.1	63.1	75.7

Abbreviations: AUC_{0-24h} = area under the concentration time curve from time 0 to 24 hours postdose; CI = confidence interval;

C_{max} = maximum measured plasma concentration; DN=dose normalized; LS = least squares

a N=24

b N=23

Source: [Study CVT-301-010 CSR Table 9](#).

Source: Applicant

REVIEWER COMMENT:

The relative bioavailability for systemic exposure to LD following administration of CVT-301 60 mg or 84 mg were 70.8% and 69.1%, respectively, of that following a single oral dose of Sinemet 25/100 when assessed by baseline-unadjusted dose-normalized-AUC0-24h, and was 53.9% and 51.3%, respectively, when assessed by baseline-unadjusted dose-normalized-Cmax.

Statistical analyses of the dose proportionality of baseline-unadjusted values of dose-normalized- AUC0-24h and dose-normalized Cmax for LD following inhaled doses of CVT-301 60 mg and 84 mg are presented in Table 6.

Table 6 Study CVT-301-010: Dose Proportionality of Inhaled Doses of CVT-301 60 mg and 84 mg LD Assessed by Dose-Normalized AUC0-24h and Cmax for LD – Unadjusted for Baseline

Dose-Normalized PK Parameter	CVT-301 Dose Level	Geometric LS Means	Ratio (%) 84 mg vs. 60 mg	90% CI for the Ratio	
				Lower (%)	Upper (%)
C _{max} (ng/mL/mg)	60 mg	8.9	95.1	85.6	105.8
	84 mg	8.4			
AUC _{0-24h} (h•ng/mL/mg)	60 mg	21.8	97.2	88.5	106.8
	84 mg	21.2			

Abbreviations: AUC_{0-24h} = area under the concentration time curve from time 0 to 24 hours postdose; CI = confidence interval;

C_{max} = maximum measured plasma concentration; LS = least squares.

Note: N=24 for C_{max}; N=23 for AUC_{0-24h}.

Source: [Study CVT-301-010 CSR Table 10](#)

Source: Applicant

REVIEWER COMMENT:

The relative bioavailability of baseline-unadjusted dose-normalized-AUC0-24h and dose-normalized Cmax following a CVT-301 84 mg dose were approximately 97% and 95%, respectively, of those following a CVT-301 60 mg dose. The 90% CIs of the ratio of the CVT-301 84 mg dose compared to the CVT-301 60 mg dose of all parameters were contained within the 80% to 125% interval.

The Office of Clinical Pharmacology concluded that the overall study design is acceptable and that the study results provide an adequate PK bridging between the to-be-marketed formulation and listed drug, Sinemet 25/100 mg oral tablets (DARRTS 12/7/2018.)

The formulations used during the clinical development program for CVT-301 for the treatment of the symptoms of OFF episodes in patients with PD are outlined in Table 7.

Table 7 Summary of CVT-301 LD Capsule Dose, Fine Particle Dose, and Dosing Regimen

Study and Development Phase	LD Dose (per capsule)	LD FPD (per capsule)	Dosing regimen	LD Capsule Dose (total)	LD FPD (total)
CVT-301-001 Phase 1	19.6 mg	10 mg	Part A: 1-5 capsules Part B: 4 capsules	Part A: 19.6/39.2/58.8/ 98 mg Part B: 78.4 mg	Part A: 10/20/30/50 mg Part B: 40 mg
CVT-301-002 Phase 2a	23.8 mg	12.5 mg	2/ 4 capsules	47.6 mg / 95.2 mg	25 mg / 50 mg
CVT-301-003 Phase 2b	27.6 mg	17.5 mg	2/ 3 capsules	55.2 mg / 82.8 mg	35 mg / 50 mg
CVT-301-004 Phase 3	30 mg / 42 mg	17.5 mg / 25 mg	2 capsules	60 mg / 84 mg	35 mg / 50 mg
CVT-301-004E Phase 3	30 mg / 42 mg	17.5 mg / 25 mg	2 capsules	60 mg / 84 mg	35 mg / 50 mg
CVT-301-005 Phase 3	30 mg / 42 mg	17.5 mg / 25 mg	2 capsules	60 mg / 84 mg	35 mg / 50 mg
CVT-301-006 Phase 1	27.6 mg / 38.8 mg	17.4 mg / 25 mg	Reference capsules: 3, 4, or 6 High fill capsules: 2	Reference capsules: 82.8/110.4/ 165.6 mg High fill capsules: 77.6 mg	Reference capsules: 50 mg / 70 mg / 105 mg High fill capsules: 50 mg
CVT-301-007 Phase 1	42 mg	25 mg	2 capsules	84 mg	50 mg
CVT-301-008 Phase 1	42 mg	25 mg	2 capsules	84 mg	50 mg
CVT-301-009 Phase 1	42 mg	25 mg	2 capsules	84 mg	50 mg
CVT-301-010 Phase 1	30 mg / 42 mg	17.5 mg / 25 mg	2 capsules	60 mg / 84 mg	35 mg / 50 mg

FPD = fine particle dose; LD = levodopa

a Number of capsules required to obtain the total LD dose (total capsule dose and target FPD).

Source: Applicant

REVIEWER COMMENT:

The to-be-marketed CVT-301 capsule used in the pivotal Phase 3 study was produced through scale-up of the formulation used in the supportive Phase 2b study. Except for optimization of some inhaler external design features, the CVT-301 dry powder inhaler remained unchanged between the supportive Phase 2b and the pivotal efficacy and safety Phase 3 studies

APPEARS THIS WAY ON ORIGINAL

Intrinsic/Extrinsic Factors

The Effects of Gender

The clinical pharmacology reviewer noted that there was a statistically significant difference between males and females in LD exposure, which was most likely due to difference in body weight; therefore, no dosing adjustment is necessary based on gender.

Effects of Smoking

The applicant conducted a Phase 1 study in smoking and non-smoking adults (Study CVT-301-007.) The C_{max} and AUC 0-24h were slightly higher in smokers compared to non-smokers; however, no dose adjustment is recommended.

Effects of Asthma

The applicant conducted a study in adults with asthma (Study CVT-301-008). The PK of LD was similar between subjects in previous studies and asthmatics subjects in Study CVT-301-008. However, due to the risk of bronchospasm in patients with asthma, the applicant is proposing not to recommend CVT-301 in this population.

The effects of renal and hepatic impairment were not specifically studied with CVT-301. The applicant is relying on safety information established with the RLD, Sinemet (Please refer to SINEMET USPI.)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

An overview of the clinical studies conducted as part of the clinical development plan of CVT-301 is outlined in Table 8.

Table 8 Overview of Clinical Studies

Study CVT-301-002 Phase 2a (completed)	Multicenter, randomized, placebo-controlled, double-blind (with respect to inhaled formulation) crossover study	Single-dose crossover	PD Subjects N = 24 CVT-301 25 mg FPD; CVT-301 50 mg FPD; Placebo; Sinemet [®] 25 mg/100 mg (CD/LD)	There were no designated efficacy parameters defined; pharmacodynamic assessments used to evaluate subject response to study treatment included: • Time to onset of meaningful ON (subject- and examiner-assessed) • Duration of an ON state (subject- and examiner-assessed) • Time to onset of dyskinesia • Duration of dyskinesia • UPDRS Part 3 score • Timed tapping test • Requirement for rescue
Study CVT-301-003 Phase 2b (completed)	Multicenter, randomized, double-blind, placebo-controlled study	4 weeks	PD Subjects N = 86 CVT-301 35 mg FPD for 2 weeks followed by CVT-301 50 mg FPD for 2 weeks; Placebo	Primary endpoint: • Mean change from predose in the average UPDRS Part 3 score at 10 to 60 minutes postdose at Week 4 Secondary endpoints: • Mean change from predose in the average UPDRS Part 3 score at 10 to 60 minutes postdose at Week 1 and Week 2 • Change and percent change from predose in UPDRS Part 3 score at specified time points postdose at each visit at each dose level • Time to objective motor response, defined as a $\geq 20\%$, $\geq 30\%$, ≥ 3-point, ≥ 6-point, and ≥ 11-point reduction from predose in the UPDRS Part 3 score at each visit at each dose level

				objective motor response at specified time points postdose at each visit at each dose level • Examiner-rated time to resolution of an OFF period to an ON state following observed treatment of subjects experiencing an OFF period at each visit at each dose level • Occurrence, duration, and severity of dyskinesia following study medication administration at each visit at each dose level • Mean daily ON time without dyskinesia, ON time with dyskinesia (troublesome and non- troublesome), and OFF time • Mean time to resolution of a treated OFF period to an ON state during the 2-week at-home period • Number and proportion of subjects achieving an objective motor response at specified time points postdose • Proportion of treated OFF periods that resolve to an ON state overall and at prespecified categorical time points
Study CVT-301-004 Phase 3 (completed)	Multicenter, 3-arm, randomized, double-blind, placebo-controlled study	12 weeks	PD Subjects N = 351 CVT-301 60 mg; CVT-301 84 mg; Placebo	Primary endpoint: • Change from predose in UPDRS Part 3 motor score at 30 minutes following treatment (84 mg) of an OFF period at Week 12 Key secondary endpoints: • Proportion of subjects achieving resolution of an OFF to an ON state within 60 minutes after administration of study drug in the clinic, maintaining the ON state at 60 minutes after administration of study drug (examiner subjective)

				assessment) • Change from predose in UPDRS Part 3 motor score at 20 minutes after administration of study drug for an OFF period • Proportion of subjects with PGI-C improvement • Change from predose in UPDRS Part 3 motor score at 10 minutes after administration of study drug for an OFF period • Change from baseline in total daily OFF time assessed by the subject (recorded in the PD Diary) for 3 consecutive days prior to Week 12
Study CVT-301-004E Phase 3 (updated full interim CSR)	Dose-level blinded, 2-arm, randomized, multicenter, long-term extension study	12 months	PD subjects previously enrolled in a CVT-301 study (CVT-301-004, CVT-301-005, CVT-301-003, or CVT-301-009) and de novo PD subjects N = 300 CVT-301 60 mg; CVT-301 84 mg	Primary endpoint was based on safety. Secondary efficacy endpoints include: • Proportion of subjects achieving resolution of an OFF to an ON state within 60 minutes after administration of study drug in the clinic, maintaining the ON state at 60 minutes after administration of study drug (examiner subjective assessment) • Subject-reported total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, assessed by the subject and recorded in the PD Diary. • Change from predose in PDQ-39 sub-scores and summary index score • Change from baseline in impact of PD Diary

Study CVT-301-005 Phase 3 (completed)	Open-label, randomized, multicenter, observational cohort controlled study	12 months	PD Subjects N = 408 CVT-301 84 mg and opportunity to down titrate to 60 mg; usual standard of care in the observational cohort	Primary and secondary endpoints were based on safety. Exploratory efficacy endpoints collected only in the CVT- 301 arm include: • Change from predose in UPDRS Part 3 motor score at 10, 20, 30, and 60 minutes following treatment of subjects experiencing an OFF period • Time curve of the UPDRS response shown as change from predose in UPDRS Part 3 motor score to 10, 20, 30 and 60 minutes following treatment of subjects experiencing an OFF period • Change from predose in the average UPDRS Part 3 score at 10 to 60 minutes following treatment of subjects experiencing an OFF period in the clinic • Proportion of patients with ≥ 3, ≥ 6, and ≥ 11 point reduction in the UPDRS Part 3 motor score from predose to postdose, at 10 to 60 minutes following treatment in the clinic (cumulative and non- cumulative) • Proportion of subjects 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) • Subject-reported total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia, and total daily ON time with troublesome dyskinesia, assessed by the subject and recorded in the PD Diary • Proportion of subjects who improved based on the
				PGI-C rating scale measured predose Exploratory efficacy endpoints collected in both CVT-301 and observational arms include: • Change from baseline visit in the PDQ-39. • Change from baseline visit in the UPDRS Part 2 score • Change from baseline visit in the S&E ADL score

Study CVT-301-009 Phase 1 (completed)	Multicenter, randomized, crossover, double- blind, placebo- controlled	Single- dose, crossover	PD Subjects N = 36 CVT-301 84 mg or placebo concurrent with Sinemet® 25 mg/100 mg (CD/LD)	Primary and secondary endpoints were based on safety. Exploratory efficacy endpoints include: Examiner rated time to ON
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Source: Applicant

5.2 Review Strategy

The evidence supporting the efficacy of CVT-301 in the treatment of OFF episodes in patients with PD is primarily from the pivotal Phase 3 study CVT-301-004, with additional information from Phase 2b study CVT-301-003. Study CVT-301-004E provides information on long term use (12 months) for both efficacy and safety.

Four Phase 3 (2 DBPC, 2OL) studies were submitted to evaluate safety of CVT-301 for the treatment of OFF episodes in patients with PD. Study CVT-301-004, in which, patients were randomized to either DL1 (60mg), DL2 (84mg) or placebo for a 12-week maintenance period, provides the most interpretable information for adverse events at the to-be-marketed dose of 84mg.

The new route of administration of levodopa, through the lungs, led the division to request studies with dedicated pulmonary function testing, Studies CVT-301-005, CVT-301-008 and study CVT-301-004E.

6 Review of Efficacy

Efficacy Summary

Study CVT-301-004

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

6.1 Indication

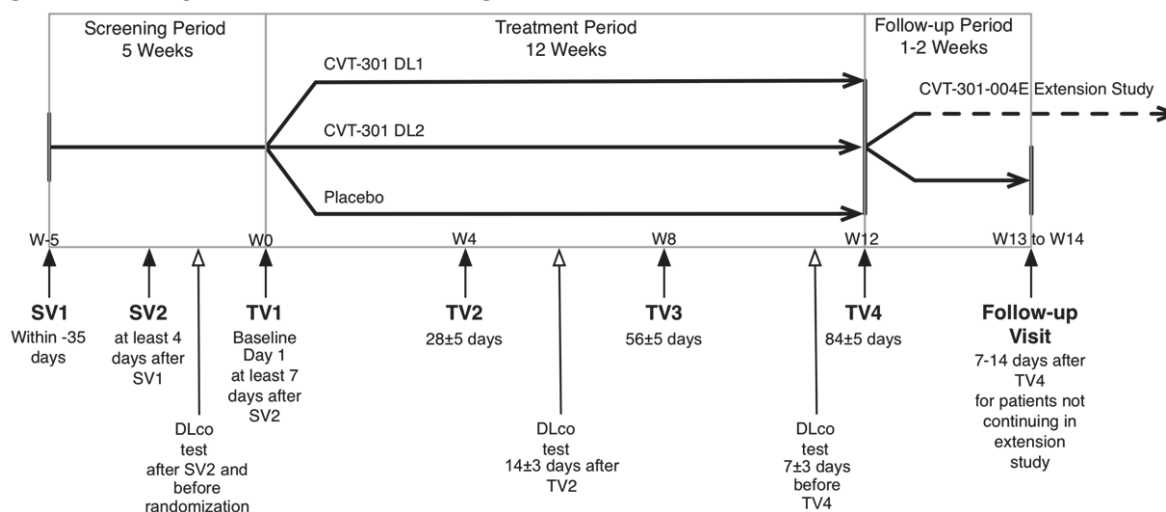
The applicant has proposed the use of CVT-301, inhaled levodopa, for the treatment of patients with Parkinson's disease who experience motor response fluctuations, OFF episodes.

6.1.1 Methods

This study was a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of inhaled CVT-301 compared with placebo in PD patients experiencing motor response fluctuations (OFF periods).

The study had 3 periods: a Screening Period, a Treatment Period, and a Follow-up Period. There were 6 to 7 planned visits: 2 Screening Period visits, 4 Treatment Period visits, and 1 Follow-up Visit (only for patients who did not continue into the extension study [CVT-301-004E] or who terminated from the study early). The individual patient planned treatment period duration was approximately 12 weeks, and the maximum anticipated study duration, including Screening and Follow-up Periods, was approximately 19 weeks. The study design is depicted in Figure 5.

Figure 5 Study CVT-301-004 Design Schematic



Abbreviations: DL1 = dose level 1; DL2 = dose level 2; DLco = carbon monoxide diffusing capacity; SV = Screening visit; TV = treatment visit; W = week. Note 1: Spirometry was performed on the same day as the DLco test.

Note 2: The baseline DLco test was scheduled after SV2 but in order to widen the window for drug shipment, protocol amendment v4.0 removed the requirement to have randomization occur after this DLco test.

Source: CVT-301-004 CSR (Appendix 16.1.1)

Source: Applicant

Eligible patients were required to have self-reported daily OFF time averaging at least 2 hours per day (not including early morning OFF time), obtained by completing the PD Patient Diary for 3 consecutive days.

Key Inclusion Criteria

Patients were required to:

- Have idiopathic PD United Kingdom (UK) PD Society Brain Bank clinical criteria
- Must be male or female subjects aged 30 to 85 years, inclusive
- Stage 1 to 3 modified Hoehn & Yahr (H&Y) scale score of PD severity
- Patients who were on a levodopa (LD)-containing therapy at least 3 times daily and must have been stable on oral LD-containing therapy for at least 2 weeks prior to (Screening Visit 1 (SV1) with a LD/ Dopa decarboxylase inhibitor (DDI)-containing regimen. Use of Rytary (or equivalent) was permitted if patients were on a stable dose for at least 6 weeks prior to SV1
- A minimum of 2 hours of average daily OFF time per waking day (excluding early morning OFF time) on the PD Patient Diary
- $A \geq 25\%$ difference between Unified Parkinson's Disease Rating Scale. (UPDRS) Part 3 scores recorded in their ON and OFF states at screening calculated as:

$$\frac{\text{OFF state value} - \text{ON state value}}{\text{OFF state value}}$$

- Perform a spirometry maneuver in the ON and OFF states and must have had a screening FEV1 $\geq 50\%$ of predicted, and an FEV1/FVC ratio $> 60\%$ in the ON state at screening.

Key Exclusion Criteria

Patients were excluded if they had:

- A previous surgery for treatment of PD including deep brain stimulation
- A history of psychotic symptoms requiring treatment, or suicidal ideation or attempt within the prior 12 months
- Chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years
- A current history of symptomatic orthostatic hypotension despite adequate treatment.

The study was conducted in the US, Canada, Poland, and Spain.

Patients were randomly assigned in a 1:1:1 ratio to receive inhaled CVT-301 Dose Level 1 (DL1; 60 mg LD), CVT-301 Dose Level 2 (DL2; 84 mg LD), or placebo. Randomization was stratified by Hoehn & Yahr scale rating category (< 2.5 versus ≥ 2.5) as measured in the ON state, to balance the severity of disease in each group, and by Screening spirometry results (FEV1 $< 60\%$ of predicted or FEV1/FVC ratio $< 70\%$ versus FEV1 $\geq 60\%$ of predicted and FEV1/FVC ratio $\geq 70\%$).

During the 12-week treatment period, patients self-administered inhaled study drug during clinic visits and as an outpatient (at home, as needed) when they experienced OFF periods (not including early morning OFF periods). Study drug could be used up to 5 times daily at home. An OFF period was to be treated with inhalation of 2 capsules of CVT-301 30 mg or 42 mg LD (ie, 2 capsules used in the inhaler per

treated period) to deliver the intended dose of 60 mg or 84 mg LD, corresponding to 35 mg or 50 mg LD FPD, respectively. The capsules for DL1 (60 mg LD), DL2 (84 mg LD), and placebo were identical in appearance to maintain blinding. The first dose of blinded inhaled study drug was administered in the clinic at Treatment Visit 1 (TV1).

Patients continued their usual prescribed standard oral PD medication regimen during participation in the study. This regimen was not to be changed for the duration of this study. Patients were NOT permitted to take PRN oral PD medications to manage OFF periods.

Spirometry was assessed at neurology sites at Screening and Baseline/TV1. After implementation of Version 4.0 of the protocol, all post-TV1 spirometry assessments were performed at a pulmonary function facility. Diffusion capacity of the lungs for carbon monoxide (DLCO) assessments was performed at dedicated pulmonary function facilities. Clinical relevance of observed changes in spirometry and DLCO results was determined by trained pulmonologists.

All patients were trained on use of the inhaler utilizing the Instructions for Use (IFU) in both the ON and OFF states during the screening visit. Prior to the first self-administration of inhaled study treatment at TV1, study staff again ensured that patients were adequately trained on the use of the inhaler. A training inhaler and sham capsules, and the IFU, were provided to patients for the inhaler training sessions. At each visit there was an optional retraining on the inhaler with patients if site staff/patients determined this was needed. Each time a patient was retrained on the inhaler, it was documented in the source documents. All patients needed to demonstrate an ability to use the inhaler while in the OFF state prior to randomization. All in-clinic dosing (in OFF state) was observed by site staff.

For at-home use, patients completed the inhaled dosing logs daily to record the use of inhaler/study medication. Any difficulties with the inhaler/study medication were self-reported by patients to the site staff. Site staff documented any difficulty in the source. Product quality complaints related to the inhaler/study medication were reported to the Applicant and investigated by the Quality Assurance Department.

Summary of Protocol CVT-301-004 Amendments

There were 5 versions of the protocol.

- Protocol versions 2 and 3 were never submitted to regulatory authorities in the United States (U.S.) or Canada and the changes were never implemented.
- Protocol version 4 contained the most extensive revisions; it added the Patient Health Questionnaire (PHQ-9) at screening and all treatment visits, for screening, monitoring and measuring the severity of depression. The Impact of Parkinson's OFF Episodes Patient Survey was also added to all treatment visits as an efficacy measure (previously only administered as a baseline test at pre-dose TV1). The UPDRS Part 4 (Questions 32-35 and 36-39) was

changed from in-clinic efficacy assessments to a safety assessment. The definition and order the key secondary endpoints was changed and the list of secondary outcomes excluded from the hierarchy was shorted and revised.

- The change from protocol versions 4 to version 5 amended the hierarchy for the endpoint analyses to add the UPDRS, Part 3 score from pre-dose to 10 minutes post treatment as the fourth key secondary endpoints. The change from baseline in total daily ON time without dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia, assessed by the patient and recorded in the PD Diary was added as the sixth and final key secondary endpoint.

The **primary efficacy variable** was:

- Change from pre-dose in UPDRS Part 3 score at 30 minutes following treatment of an OFF period at TV4 (Week 12)

Key secondary variables were:

- Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after administration of study drug in the clinic, maintaining the ON state at 60 minutes after administration of study drug (examiner subjective assessment) at TV4
- Change from pre-dose in UPDRS Part 3 score at 20 minutes after administration of study drug for an OFF period at TV4
- Proportion of patients with pre-dose PGI-C improvement (ie, much improved, improved, a little improved) at TV4
- Change from pre-dose in UPDRS Part 3 score at 10 minutes after administration of study drug for an OFF period at TV4
- Change from baseline in total daily OFF time assessed by the patient (recorded in the PD Patient Diary) for 3 consecutive days prior to TV4

6.1.2 Demographics

The demographic and baseline characteristics for the ITT population are presented in Table 9 below.

Table 9 Study CVT-301-004 Demographic and Baseline Characteristics (ITT Population)

Characteristic	Statistic	Placebo	CVT-301	CVT-301	Overall
Age (years)	n	112	113	114	339
	Mean (SD)	62.6 (8.83)	63.9 (9.24)	63.5 (7.97)	63.3 (8.69)
	Median	65.0	66.0	64.0	65.0
	Min, Max	38, 80	40, 82	45, 82	38, 82
Age (years)					
< 65	n (%)	55 (49.1)	54 (47.8)	58 (50.9)	167 (49.3)
≥ 65	n (%)	57 (50.9)	59 (52.2)	56 (49.1)	172 (50.7)
Gender					
Male	n (%)	86 (76.8)	80 (70.8)	83 (72.8)	249 (73.5)
Female	n (%)	26 (23.2)	33 (29.2)	31 (27.2)	90 (26.5)
Race					
White	n (%)	107 (95.5)	107 (94.7)	107 (93.9)	321 (94.7)
Black or African American	n (%)	0	3 (2.7)	4 (3.5)	7 (2.1)
Asian	n (%)	4 (3.6)	0	2 (1.8)	6 (1.8)
Other	n (%)	1 (0.9)	2 (1.8)	1 (0.9)	4 (1.2)
Native Hawaiian or other Pacific Islander	n (%)	0	1 (0.9)	0	1 (0.3)
Body Mass Index (kg/m ²) ^a					
	n	112	113	114	339
	Mean (SD)	27.63 (5.328)	27.19 (4.807)	27.43 (4.664)	27.42 (4.928)
	Median	26.95	26.70	26.90	26.90
	Min, Max	18.9, 47.4	17.4, 40.1	18.7, 42.9	17.4, 47.4
Country					
United States	n (%)	81 (72.3)	86 (76.1)	81 (71.1)	248 (73.2)
Poland	n (%)	19 (17.0)	18 (15.9)	29 (25.4)	66 (19.5)
Canada	n (%)	9 (8.0)	9 (8.0)	2 (1.8)	20 (5.9)
Spain	n (%)	3 (2.7)	0	2 (1.8)	5 (1.5)
Smoking History					
Never	n (%)	72 (64.3)	75 (66.4)	65 (57.0)	212 (62.5)
Former	n (%)	37 (33.0)	38 (33.6)	44 (38.6)	119 (35.1)
Current	n (%)	3 (2.7)	0	5 (4.4)	8 (2.4)
MMSE Total Score					
	n	112	113	114	339
	Mean (SD)	28.8 (1.46)	28.6 (1.46)	29.0 (1.30)	28.8 (1.41)
	Median	29.0	29.0	29.5	29.0
	Min, Max	25, 30	25, 30	25, 30	25, 30
Screening Spirometry					
FEV1 < 60% or FEV1/FVC ratio < 70%	n (%)	6 (5.4)	6 (5.3)	7 (6.1)	19 (5.6)

FEV1 $\geq$ 60% and FEV1/FVC ratio $\geq$	n (%)	106 (94.6)	107 (94.7)	107 (93.9)	320 (94.4)
Baseline PD Severity					
Hoehn & Yahr stage < 2.5	n (%)	74 (66.1)	74 (65.5)	72 (63.2)	220 (64.9)
Hoehn & Yahr stage $\geq$ 2.5	n (%)	38 (33.9)	39 (34.5)	42 (36.8)	119 (35.1)
Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ITT = intent-to-treat; LD = levodopa; Max = maximum; Min = minimum; MMSE = Mini Mental State Examination; PD = Parkinson's disease; SD = standard deviation.					
^a Body mass index was calculated as [weight (kg)] / [height (m)] ² . Source: Table 14.1.3.1.2 .					
Source: Applicant					

REVIEWER COMMENT:

The key demographics (age, race, gender, smoking status and locality) disease severity indicators (Hoehn and Yahr, MMSE) and pulmonary function status were similar across treatment cohorts. The majority of patients were from sites in the U.S. ranging from 72 to 76%. The study population was approximately 95% white and approximately two-thirds of patients never smoked, one-third was former smokers and 0 to 4.4% were current smokers. Seventy percent to 76% of study subjects were men, which is slightly higher than the prevalence of PD by gender reported in the published literature. Approximately 65% of patients had Hoehn and Yahr < stage 2.5 and MMSE of 29. FEV1/FVC ratio was approximately 94%.

6.1.3 Subject Disposition

Disposition of Patients

The disposition of subjects for the study is presented in Table 10.

Table 10 Number of Patients Enrolled and Study Termination (All Available Population)

	Placebo n (%)	CVT- 301 DL1 n (%)	CVT- 301 DL2 n (%)	Total n (%)
Screened				498
Failed Screening ^a				147 (29.5)
Randomized ^a	116	115	120	351 (70.5)

Randomized Not Dosed ^b	4 (3.4)	2 (1.7)	6 (5.0)	12 (3.4)
Safety Population^b	112 (96.6)	113 (98.3)	114 (95.0)	339 (96.6)
Came in for TV1 ^c	112 (100)	113 (100)	114 (100)	339 (100)
Came in for TV2 ^c	103 (92.0)	103 (91.2)	109 (95.6)	315 (92.9)
Came in for TV3 ^c	97 (86.6)	99 (87.6)	102 (89.5)	298 (87.9)
Came in for TV4 ^c	97 (86.6)	99 (87.6)	97 (85.1)	293 (86.4)
Completed Study ^c	97 (86.6)	96 (85.0)	97 (85.1)	290 (85.5)
Withdrawn from Study ^c	15 (13.4)	17 (15.0)	17 (14.9)	49 (14.5)
Reason for Withdrawal from Study ^d				
Patient Withdrew Consent	10 (66.7)	9 (52.9)	9 (52.9)	28 (57.1)
Adverse Event	3 (20.0)	3 (17.6)	6 (35.3)	12 (24.5)
Other	2 (13.3)	2 (11.8)	1 (5.9)	5 (10.2)
Lack of Efficacy	0	1 (5.9)	1 (5.9)	2 (4.1)
Lost to Follow-up	0	2 (11.8)	0	2 (4.1)
Roll over to CVT-301-004E ^c				
Yes	83 (74.1)	74 (65.5)	79 (69.3)	236 (69.6)
No	16 (14.3)	26 (23.0)	21 (18.4)	63 (18.6)
Missing ^e	13 (11.6)	13 (11.5)	14 (12.3)	40 (11.8)

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; LD=levodopa; TV = Treatment Visit.

^a Percentages are based on the number of screened patients.

^b Percentages are based on the number of randomized patients.

^c Percentages are based on the number of patients in the safety population.

^d Percentages are based on the number patients in the safety population withdrawn from study.

^e Not specified by patient at the time of database

lock. Source: Table 14.1.1.1.

Source: Applicant

REVIEWER COMMENT:

Of 498 patients who were screened, 351 patients were randomized and 339 patients received at least one dose of study drug, while 147 patients failed screening(pulmonary related criteria, did not have motor fluctuations for a minimum of 2 hours, did not have >25% difference in UPDRS part 3 score between ON and OFF state had a condition that in Investigator's opinion would make patients unable to comply with study, had MMSE score <25) Of the 339 patients randomized who received at least one dose of study drug, 49 (14%) withdrew from the study (withdrew consent, adverse event, lack of efficacy). Withdrawal for adverse event was highest in the DL 2 (35%) versus DL 1 (17.6%) and placebo (20%).

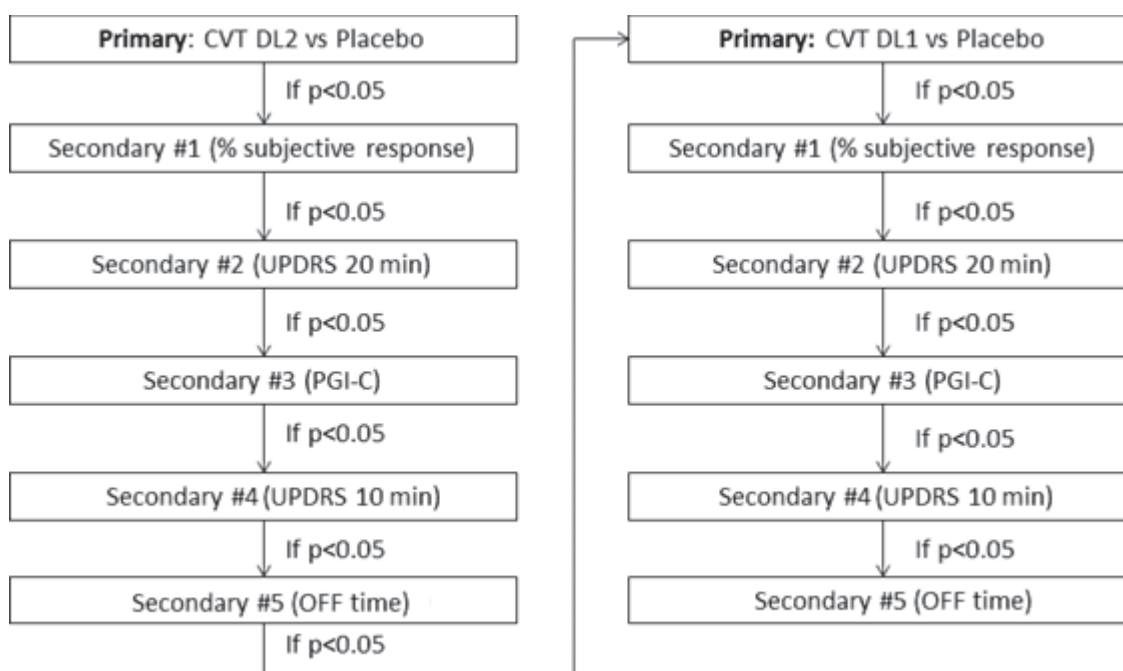
6.1.4 Analysis of Primary Endpoint(s)

The trial had one primary efficacy endpoint and 5 key secondary efficacy endpoints.

- **Primary efficacy endpoint:** change from pre-dose in the UPDRS part 3 motor function score at 30 minutes post-dose at TV4.
- **Key secondary efficacy endpoint 1:** proportion of patients achieving resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment.
- **Key secondary efficacy endpoint 2:** change from pre-dose in the UPDRS part 3 motor score at 20 minutes post-dose at TV4.
- **Key secondary efficacy endpoint 3:** proportion of patients who improved in the Patient Global Impression of Change (PGI-C) score at TV4.
- **Key secondary efficacy endpoint 4:** change from baseline to TV4 in patient-recorded total daily OFF time.
- **Key secondary efficacy endpoint 5:** change from pre-dose in the UPDRS part 3 motor score at 10 minutes post-dose at TV4.

Two dose levels were included in the study, DL1 (60mg) and DL2 (84mg). A hierarchical testing approach (Figure 6) was used for the analyses of the primary and key secondary variables to control the overall type I error rate at 0.05. First, the CVT-301 high dose (CVT-301 DL2) and placebo were compared on the 6 endpoints (presented above.) If the primary endpoint was statistically significant ($p < 0.05$), then the remaining comparisons were tested in order, so that each endpoint could be declared to be statistically significant only if the nominal p-value from all the previously tested endpoints were also less than 0.05. Next, the CVT-301 low dose (CVT-301 DL1) and placebo were compared in the same order with the same hierarchical rules.

Figure 6 Hierarchy for Primary and Key Secondary Endpoints



Source: Applicant

The treatment difference between the two arms was estimated using a mixed model for repeated measurements (MMRM) with a contrast. The model uses measurements on the primary efficacy endpoint at each post-baseline visit (TV2, TV3, TV4) as the dependent variable and includes treatment group (placebo, CVT-301 60mg [DL1] and CVT-301 84mg [DL2] placebo), visit (TV2, TV3 and TV4), interaction between treatment group and visit, stratification variables (Hoehn and Yahr scale rating and screening FEV1 spirometry score), baseline OFF-state UPDRS part 3 score as fix-effect covariates and patients as a random-effect covariate. An unstructured covariance structure was applied for MMRM using the Kenward-Roger method for a denominator degrees of freedom calculation.

The least square (LS) mean, standard error, and LS mean difference between CVT-301 and placebo at TV4 and 95% confidence interval (CI), as well as the p-value for the hypothesis testing were calculated.

The original version of the Statistical Analysis Plan, dated 15 October 2015, was amended before database lock. The final SAP, dated 05 January 2017, is in Appendix 16.1.9. No changes were made to the SAP after database lock. Version 1.0 of the SAP (15 October 2015) corresponded to Version 4.0 of the protocol. Version 2.0 of the SAP (the final version), dated 05 January 2017, corresponded to Version 5.1 of the protocol.

Primary Efficacy Endpoint

The applicant's results for the primary efficacy endpoint was independently confirmed by the FDA statistical reviewer (Sungwon Lee, PhD, DARRTS 9/9/2018.)

The primary efficacy endpoint for CVT-301 84mg versus placebo is presented in Table 11.

Table 11 Evaluation on the primary efficacy endpoint for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301
Least square mean difference (mean change in CVT-301 84mg – mean change in	-3.92
95% confidence interval	(-6.84, -1.00)
P-value	0.009

Source: Statistical Reviewer

REVIEWER COMMENT:

The primary endpoint, change in UPDRS part 3 from pre-dose to 30 minutes post dose at visit 4 was statistically significant at $p < 0.009$.

Key Secondary Endpoints

The key secondary endpoints for **CVT-301 84mg** are presented in Tables 12-16 below.

- **Key secondary efficacy endpoint 1:** proportion of patients achieving resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment.

Table 12 Key Secondary #1 DL2 (84mg)

Statistics	Placebo vs CVT-301 84mg
Common odds ratio (odds in CVT-301 84mg / odds in placebo)	2.4
95% confidence interval	(1.35, 4.26)
P-value	0.003

Source: Statistical Reviewer

- **Key secondary efficacy endpoint 2:** change from pre-dose in the UPDRS part 3 motor score at 20 minutes post-dose at TV4.

Table 13 Key Secondary #2 DL2 (84mg)

Statistics	Placebo vs CVT-301 84mg
------------	-------------------------

Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-2.55
95% confidence interval	(-5.22, 0.13)
P-value	0.062

Source: Statistical Reviewer

- **Key secondary efficacy endpoint 3:** proportion of patients who improved in the Patient Global Impression of Change (PGI-C) score at TV4.

Table 14 Key Secondary #3 DL2 (84mg)

Statistics	Placebo vs CVT-301 84mg
Common odds ratio (odds in CVT-301 84mg / odds in placebo)	2.85
95% confidence interval	(1.56, 5.13)
(P value	<0.001

Source: Adapted from Statistical Reviewer

- **Key secondary efficacy endpoint 4:** change from baseline to TV4 in patient-recorded total daily OFF time.

Table 15 Key Secondary #4 DL2 (84mg)

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	0.01
95% confidence interval	(-0.55, 0.56)
(P value	0.046

Source: Adapted from Statistical Reviewer

- **Key secondary efficacy endpoint 5:** change from pre-dose in the UPDRS part 3 motor score at 10 minutes post-dose at TV4.

Table 16 Key Secondary #5 DL2 (84mg)

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-2.26
95% confidence interval	(-4.48, -0.04)
(P value	0.975

Source: Adapted from Statistical Reviewer

REVIEWER COMMENT:

Each of the Key Secondary Efficacy Endpoint results was independently confirmed by the FDA Statistical Reviewer. Only the first key secondary endpoint, resolution of an OFF to an ON state within 60 minutes of administration of study drug in the clinic, maintaining the ON at 60 minutes after study drug administration at TV4 (examiner subjective assessment), was statistically significant. The second key secondary efficacy endpoint, change

from Pre dose in UPDRS Part 3 at 20 minutes was not clinically significant; therefore, results of subsequent key secondary efficacy endpoints in the hierarchical testing order are not considered statistically significant. Percentage of patients improved on PGI-C and change from pre dose UPDRS part 3 at 10 minutes were nominally significant.

In addition to the key secondary efficacy endpoints, DL1 (60mg mg) versus placebo was analyzed for efficacy endpoint Pre dose in UPDRS part 3 at 30 minutes Post Dose at treatment visit 4, Table 17.

Table 17 The Change on the UPDRS Part III at 30 minutes Compared to Placebo at TV4 for CVT 301 DL1 (60mg)

Statistics	Placebo vs CVT-301 60mg
Least square mean difference (mean change in CVT-301 60mg – mean change in placebo)	-3.07
95% confidence interval	(-5.99, -0.16)
(P value	0.039)

Source: Statistical Reviewer

REVIEWER COMMENT:

The treatment difference was in favor of improvement associated with CVT 301 DL1, However, the treatment difference for the 84 mg dose was numerically greater for the efficacy endpoint, change in UPDRS part 3 pre dose to 30 minutes post dose.

Sensitivity Analyses

During the filing review, Site 5301 located in Poland, was identified as possibly having driven the large efficacy in the study. With 12 observations from site 5301 removed from the primary efficacy endpoint analysis, the difference in mean change of UPDRS part 3 score pre-and post-dose, between CVT-301 84mg and placebo, decreased from 3.9 to -2.9 and its p-value from 0.009 to 0.046.

A closer look at the data from Site 5301 revealed large effect on the primary efficacy endpoint for patients in CVT-301 84mg arm and the best case (zero efficacy) for patients in placebo arm as shown in Table 18.

Table18. Details of the Site 5301 data

Site	Visit	ID	Treatment arm	UPDRS score change
		CVT-301-004 (b) (6)	Placebo	0
		CVT-301-004	Placebo	-12

5301	TV4	CVT-301-004	(b) (6)	Placebo	0
		CVT-301-004		CVT-301 84mg	-20
		CVT-301-004		CVT-301 84mg	-25
		CVT-301-004		CVT-301 84mg	-16
		CVT-301-004		CVT-301 84mg	-26
		CVT-301-004		CVT-301 84mg	-25

Source: Statistical Reviewer

To assess the effect of this site on the study result, the statistical reviewer conducted sensitivity analyses using the pattern mixture model under two sensible missing data scenarios.

Sensitivity analysis under scenario 1 assumes that progression trajectories of patients in Site 5301 of Poland follows progression trajectories of patients in their respective arm in North America, which does not seem to have site issues, instead of their own region Europe, e.g., a treatment trajectory of a patient in Site 5301 assigned in a placebo arm is similar to that of a patient in a placebo arm in North America given their baseline characteristics and assessment values before dropping out.

Table 19 summarizes the sensitivity analysis results.

Table 19 Sensitivity analysis 1 to assess the effect of the Site 5301 issue

Statistics	Placebo vs CVT-301
Least square mean difference (mean change in CVT-301 84mg – mean change in	-3.37
95% confidence interval	(-6.32, -0.42)
P-value	0.025

Source: Statistical Reviewer

Sensitivity analysis under scenario 2 assumes that progression trajectories of patients in Site 5301 follows progression trajectories of patients in their respective arm in the Europe, e.g., a treatment trajectory of a patient in Site 5301 assigned in a placebo arm is similar to that of a patient in a placebo arm in European sites given their baseline characteristics and assessment values before dropping out from the study. Table 20 summarizes the sensitivity analysis results.

Table 20 Sensitivity analysis 2 to assess the effect of the Site 5301 issue

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.10
95% confidence interval	(-6.16, -0.03)
P-value	0.048

Source: Statistical Reviewer

In addition, sensitivity analyses were conducted to assess:

- The effect of violation of missing data assumption[®]: (Table 21)

Table 21 Sensitivity analysis to assess the effect of violation of the missing data assumption

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.83
95% confidence interval	(-6.74, -0.94)
P-value	0.009

Source: Statistical Reviewer

Sensitivity analysis under this placebo-based assumption, as summarized in Table 21, provides statistically significant evidence for treatment difference between placebo and CVT-301 84mg.

REVIEWER COMMENT:

The results from each of the model-based sensitivity analyses of the primary efficacy endpoint were very similar to that from the primary analysis (i.e., statistically significant results for MMRM ANCOVA model based on overall ITT population).

6.1.7 Subpopulations

Pre-specified Subgroup analyses

Subgroup analyses were completed for demographic and baseline characteristics.

FDA Statistical Reviewer results of subgroup analyses are presented below.

Age, Gender and Race

Since 95% of the ITT population for the primary analysis is white, a subgroup analysis for race was not conducted (Table 22).

Table 22 Subgroup analysis for age, gender and region

Subgroup		Size	Placebo vs CVT-301 84mg, LS mean difference (95% CI)
Age	<65	167	-3.08 (-7.72, 1.56)
	≥65	172	-4.20 (-7.81, -0.59)
Gender	Female	90	-0.57 (-6.81, 5.67)
	Male	249	-4.61 (-7.95, -1.26)
Region	North America	268	-3.13 (-5.78, -0.49)

	Europe	71	-4.79 (-12.61, 3.03)
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Source: Statistical Reviewer

REVIEWER COMMENT:

The effect size for study drug CVT-301 DL2 (84mg) is smaller in female Parkinson's disease patients; however, the sample size for females is smaller than males (90 versus 249.)

Hoehn & Yahr scale, PFTs, Baseline OFF-state UPDRS part 3 score

These subgroups were chosen as possible confounding factors and were included in the primary statistical method (MMRM) as control variables (Table 23).

Table 23 Subgroup analysis for other special populations

Subgroup		Size	Placebo vs CVT-301 84mg, LS mean difference (95% CI)
Hoehn & Yahr scale	<2.5	220	-2.49 (-6.13, 1.15)
	≥2.5	119	-6.66 (-11.67, -1.64)
FEV1 spirometry score	<60%	19	-7.68 (-16.25, 0.90)
	≥60%	320	-3.72 (-6.77, -0.67)
Baseline OFF-state UPDRS part 3 score	≤28	111	-3.88 (-7.88, 0.12)
	29 to 37	108	-6.69 (-10.97, -2.41)
	≥38	120	-1.55 (-8.34, 5.24)

Source: Statistical Reviewer

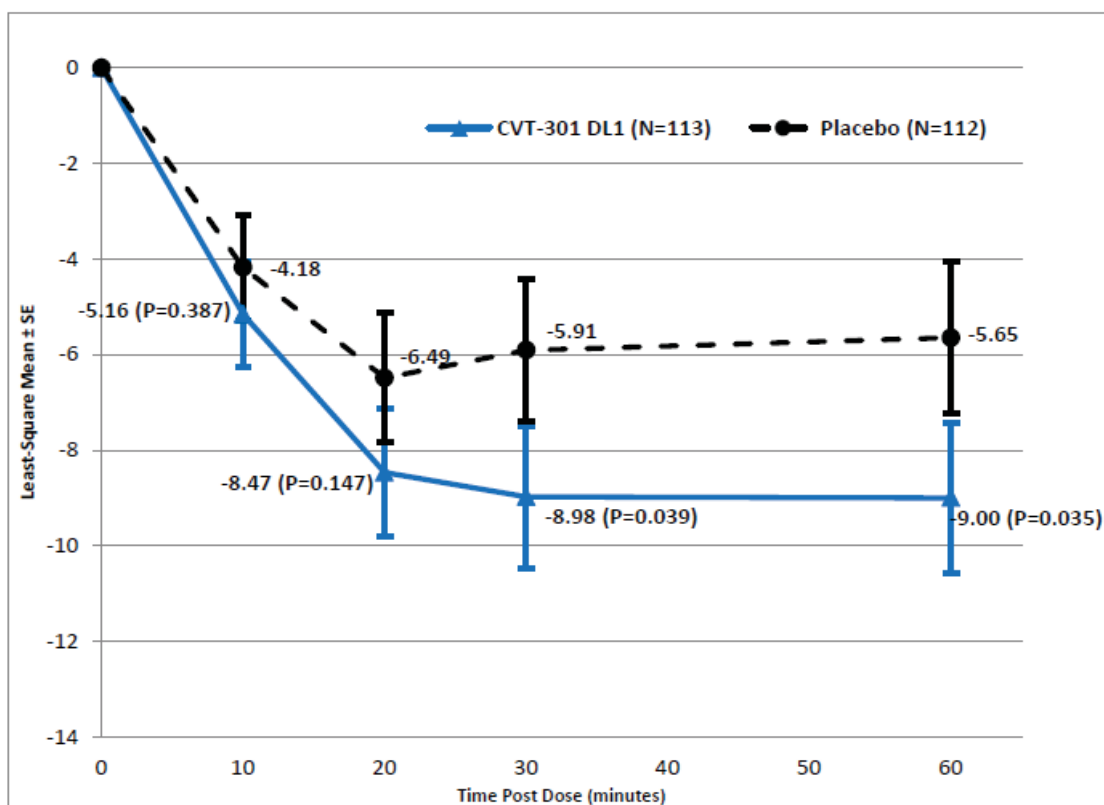
REVIEWER COMMENT:

The treatment effect of CVT-301 DL2 (84mg) appears larger in the subgroup with Hoehn & Yahr scale ≥ 2.5 and baseline OFF-state UPDRS part 3 score of 29 to 37.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant assessed change in UPDRS part 3 from pre dose to post dose at 10 minute intervals for 60 minutes, for DL1 and DL2 (Figures 7 and 8.)

Figure 7 CVT-301 DL1 versus Placebo: Change from Pre-dose in UPDRS Part 3 Score by Time Point at Treatment Visit 4



Abbreviations: CVT-301 DL2 = 84 mg LD; LD = levodopa; SE = standard error; TV = treatment visit; UPDRS

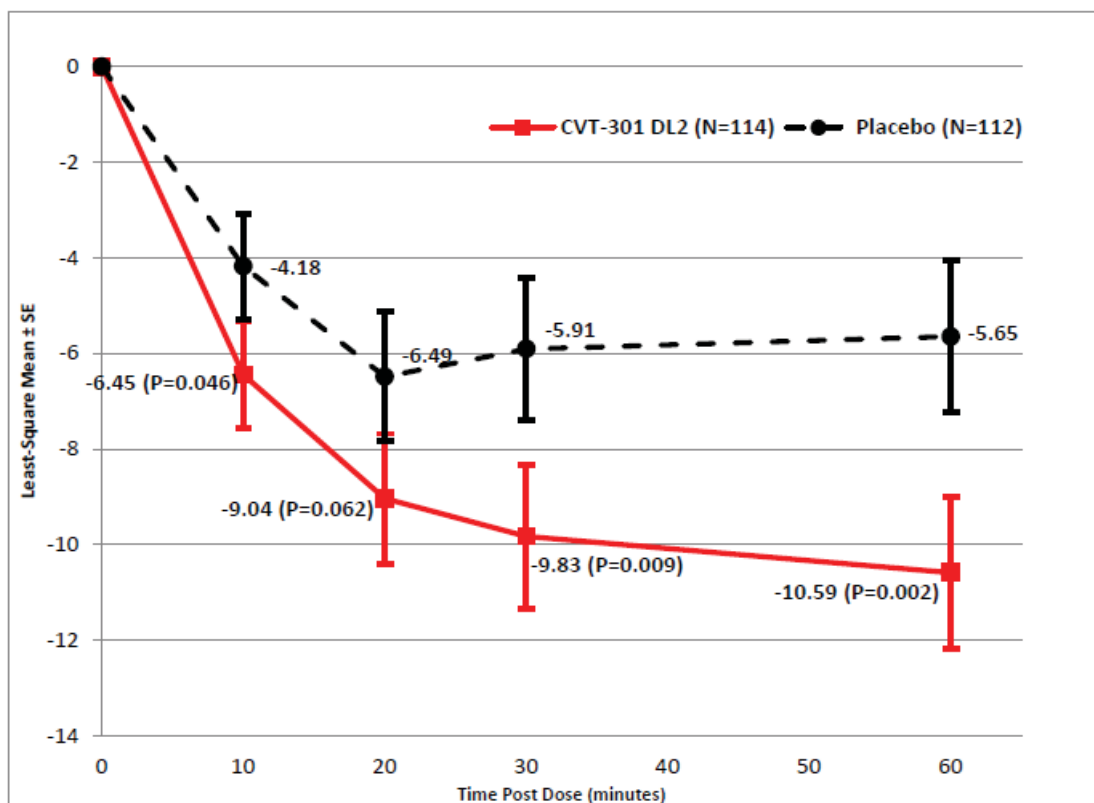
= Unified Parkinson's Disease Rating Scale.

Notes: The mixed model for repeated measures included the treatment group (CVT-301 DL2, CVT-301 DL1, or placebo), visit (TV2, TV3, TV4), the stratification variables (baseline Hoehn & 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

OFF-state baseline UPDRS Part 3 score was included as a covariate, assuming an unstructured covariance matrix. A separate mixed model for repeated measures was fitted for each of the time points. Source: [Table 14.2.3.1.1](#)

Source: Applicant

Figure 8 CVT-301 **DL2 versus Placebo: Change from Pre-dose in UPDRS Part 3 Score by Time Point at Treatment Visit 4**



Abbreviations: CVT-301 DL2 = 84 mg LD; LD = levodopa; SE = standard error; TV = treatment visit; UPDRS

= Unified Parkinson's Disease Rating Scale.

Notes: The mixed model for repeated measures included the treatment group (CVT 301 DL2, CVT-301 DL1 or placebo), visit (TV2, TV3, TV4), the stratification variables (baseline Hoehn & 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

OFF-state baseline UPDRS Part 3 score was included as a covariate, assuming an unstructured covariance matrix. A separate mixed model for repeated measures was fitted for each of the time points. Source: [Table 14.2.3.1.1](#)

Source: Applicant

REVIEWER COMMENT:

The change in OFF symptoms was measured up to 60 minutes post-dose and was shown to have the largest treatment difference at 60 minutes for DL1 and DL2.

Additional Efficacy Studies:

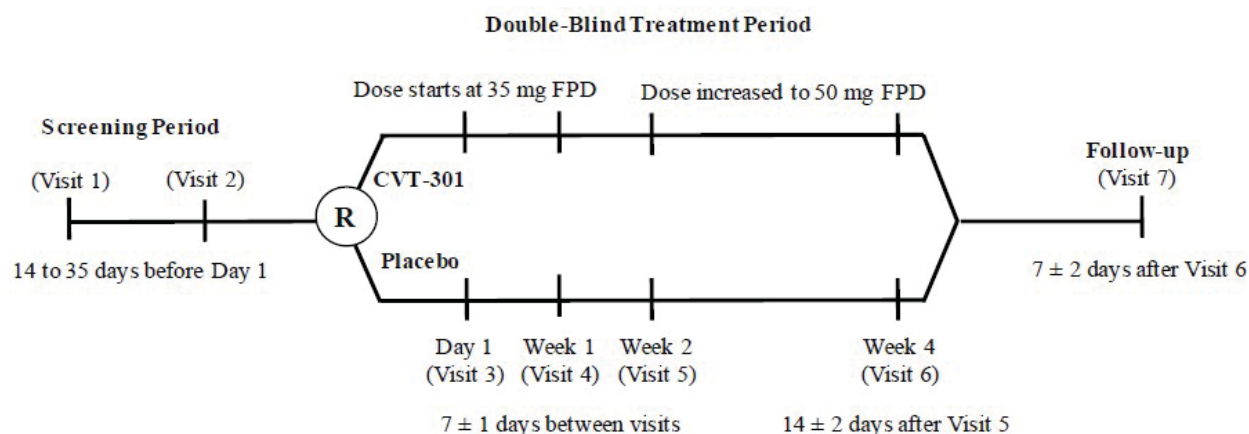
Study CVT-301-003 (Phase 2b)

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy and Safety of Inhaled CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients with Motor Response Fluctuations (OFF Phenomena)

Methods:

This study was a randomized, double-blind, placebo-controlled, multicenter study of inhaled CVT-301 or placebo for the treatment of up to 3 OFF episodes per day in PD subjects experiencing motor fluctuations (OFF episodes). The study had 3 periods (screening period, treatment period, and follow-up period) and a total of 7 planned visits (2 screening visits, 4 treatment visits, and 1 follow-up visit). For each subject, the planned treatment period was approximately 4 weeks, and the study duration ranged from approximately 8 to 10 weeks. No changes in the dose or standard dosing schedule of a subject's usual PD medications were permitted from screening until the final study visit. The design is depicted in Figure 9.

Figure 9 Design:



Source: Applicant

Primary Efficacy Assessments

The primary efficacy assessment was the effect of 50 mg FPD (84mg) CVT-301 versus placebo on mean change from pre-dose in the **average** UPDRS Part 3 score obtained over 10 to 60 minutes post-dose. The primary endpoint of the study was based on the evaluation of this assessment at Visit 6 (Week 4).

Demographics

The demographic information is summarized in Table 24.

Table 24 Demographics Study CVT-301-003

Characteristic	Statistic	Place bo	CVT-301 (N=43)	Total (N=86)
Age (years)	n	43	43	86
	Mean	62.7	62.0	62.4
	SD	9.08	8.36	8.68
	Median	63.0	62.0	62.5
	Min, Max	43, 79	37, 77	37, 79
Gender				
Male	n (%)	32 (74.4)	25 (58.1)	57 (66.3)
Female	n (%)	11 (25.6)	18 (41.9)	29 (33.7)
Ethnicity				
Hispanic or Latino	n (%)	3 (7.0)	2 (4.7)	5 (5.8)
Not Hispanic or Latino	n (%)	40 (93.0)	41 (95.3)	81 (94.2)
Race				
American Indian or Alaska Native	n (%)	0	1 (2.3)	1 (1.2)
Asian	n (%)	1 (2.3)	1 (2.3)	2 (2.3)
Black or African American	n (%)	0	0	0
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	42 (97.7)	41 (95.3)	83 (96.5)
Other	n (%)	0	0	0
Height (cm)	n	43	43	86
	Mean	173.76	169.65	171.71
	SD	8.663	10.290	9.678
	Median	175.00	171.00	172.70
	Min, Max	152.4, 190.5	149.9, 186.0	149.9, 190.5
Weight (kg)	n	43	43	86
	Mean	83.17	74.24	78.70
	SD	14.256	15.214	15.329
	Median	82.60	72.10	78.00
	Min, Max	54.4, 116.1	42.3, 110.6	42.3, 116.1
BMI ^a (kg/m ²)	n	43	43	86
	Mean	27.56	25.70	26.63
	SD	4.627	4.233	4.507
	Median	26.20	25.20	25.80
	Min, Max	21.1, 40.4	16.5, 37.6	16.5, 40.4
Country				
GBR	n (%)	2 (4.7)	2 (4.7)	4 (4.7)
ITA	n (%)	5 (11.6)	5 (11.6)	10 (11.6)
SRB	n (%)	4 (9.3)	4 (9.3)	8 (9.3)
USA	n (%)	32 (74.4)	32 (74.4)	64 (74.4)
Region				
United States	n (%)	32 (74.4)	32 (74.4)	64 (74.4)
Europe	n (%)	11 (25.6)	11 (25.6)	22 (25.6)
Smoking History				
Never	n (%)	31 (72.1)	27 (62.8)	58 (67.4)
Former	n (%)	11 (25.6)	14 (32.6)	25 (29.1)
Current	n (%)	1 (2.3)	2 (4.7)	3 (3.5)

Number of Pack-years (Former and Current Smokers)	n	12	16	28
	Mean	10.992	6.366	8.348
	SD	9.2603	7.6859	8.5551
	Median	9.000	2.500	5.500
	Min, Max	0.15, 28.00	0.25, 25.00	0.15, 28.00
MMSE Total Score	n	43	43	86
	Mean	29.2	28.9	29.1
	SD	1.05	1.42	1.25
	Median	30.0	30.0	30.0
	Min,	27, 30	25, 30	25, 30

Abbreviations: BMI = body mass index; GBR = Great Britain; ITA = Italy; ITT = intent-to-treat; max = maximum; min = minimum; MMSE = Mini-Mental State Examination; SD = standard deviation; SRB = Serbia; USA = United States of America.

^a BMI was calculated as weight (kg)/[height (m)]².

Source: [Table 14.1.2.1](#).

Source: Applicant

REVIEWER COMMENT:

The males and females were evenly distributed in the drug group compared to placebo and the BMI was on average lower in the drug group compared to placebo. The study population was 95% white and 74% of the patients were enrolled at sites in the U.S.

Disposition

Subject disposition is summarized in the table below (Table 25).

Table 25 Subject Disposition (All Available Subjects)

	Placebo n (%)	CVT-301 n (%)	Total n
Screened			134
Failed screening			45 (33.6)
Randomized ^a	45	44	89 (66.4)
Completed study ^b	36 (80.0)	39 (88.6)	75 (84.3)
Withdrawn from study ^b	9 (20.0)	5 (11.4)	14 (15.7)
Reason for withdrawal from study ^c			
Adverse event	3 (33.3)	2 (40.0)	5 (35.7)
Death	0	0	0
Subject withdrew consent	5 (55.6)	3 (60.0)	8 (57.1)
Protocol violation	0	0	0
Lost to follow-up	1 (11.1)	0	1 (7.1)
Other	0	0	0

Withdrawn from study before receiving any study drug ^b	2 (4.4)	1 (2.3)	3 (3.4)
Randomized and dosed ^a	43	43	86 (64.2)
Safety population ^d	43 (100)	43 (100)	86 (100)
ITT population ^d	43 (100)	43 (100)	86 (100)
Per-protocol population ^d	40 (93.0)	39 (90.7)	79 (91.9)
Completer population ^d	36 (83.7)	36 (83.7)	72 (83.7)
Completed ^d Visit 3	43 (100)	43 (100)	86 (100)
Completed ^d Visit 4	40 (93.0)	42 (97.7)	82 (95.3)
Completed ^d Visit 5	39 (90.7)	40 (93.0)	79 (91.9)
Completed ^d Visit 6	36 (83.7)	39 (90.7)	75 (87.2)
Completed ^d Visit 7	42 (97.7)	43 (100)	85 (98.8)
Completed study ^d	36 (83.7)	39 (90.7)	75 (87.2)
Withdrawn from study ^d	7 (16.3)	4 (9.3)	11 (12.8)
Reason for withdrawal from study ^e			
Adverse event	3 (42.9)	1 (25.0)	4 (36.4)
Death	0	0	0
Subject withdrew consent	3 (42.9)	3 (75.0)	6 (54.5)
Protocol violation	0	0	0
Lost to follow-up	1 (14.3)	0	1 (9.1)
Other	0	0	0

Abbreviation: ITT = intent-to-treat.

^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 subjects withdrawn from study.

^d Percentages are based on the number of randomized and dosed subjects.

^e Percentages are based on the number of randomized and dosed subjects withdrawn from study.

Source: [Table 14.1.1](#).

Source: Applicant

REVIEWER COMMENT:

A greater number of patients in the placebo group withdrew from the study compared to patients in the active drug group.

Analysis of Primary Endpoint

The **primary efficacy endpoint** was the mean change from pre-dose in the UPDRS Part 3 score at 10 to 60 minutes post-dose at Visit 6 (Week 4).

The primary efficacy endpoint was analyzed by a mixed model for repeated measurements (MMRM). The MMRM used mean change from pre-dose in the UPDRS Part 3 score at 10 to 60 minutes post-dose at each post-baseline visit (Visits 4, 5, and 6) as the dependent variable, and included baseline PD severity (Low, High), country, treatment, visit, and treatment-by- visit interaction as fixed factors and

baseline UPDRS Part 3 score, screening score in OFF state, as a covariate. The least squares (LS) mean, standard error (SE), and LS mean difference between CVT-301 and placebo group at Visit 6; along with the 95% confidence interval (CI) were provided.

The results of the primary efficacy endpoint are presented in Table 26.

Table 26 Change from Pre dose in Average UPDRS Part 3 Score 10 to 60 Minutes Post dose at Visit 6: CVT-301 50 mg FPD Versus Placebo (Study CVT-301-003 ITT Population)

Study Visit	Placebo (N =	CVT-301 50 mg FPD
Visit 6 (CVT-301 50 mg FPD), n	40	42
LS Mean	-3.07	-10.02
SE (LS Mean)	1.544	1.503
95% CI (LS Mean)	(-6.14, 0.01)	(-13.01, -7.02)
LS Mean Difference (CVT-301 – placebo)		-6.95
95% CI (LS Mean Difference)		(-10.31, -3.60)
P-value (LS Mean Difference)		<0.001
p-value (LS Mean Difference)		<0.001

Abbreviations: CI = confidence interval; FPD = fine particle dose; ITT = intent-to-treat; LS = least square; MMRM = mixed model repeated measures; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale

Note: All results based on a MMRM analysis. n is # of subjects with available data (missing data was implicitly imputed via the MMRM).

Source: [Study CVT-301-003 CSR Table 14.2.1.1](#) and [Table 14.2.2.2.1](#)

Source: Applicant

REVIEWER COMMENT:

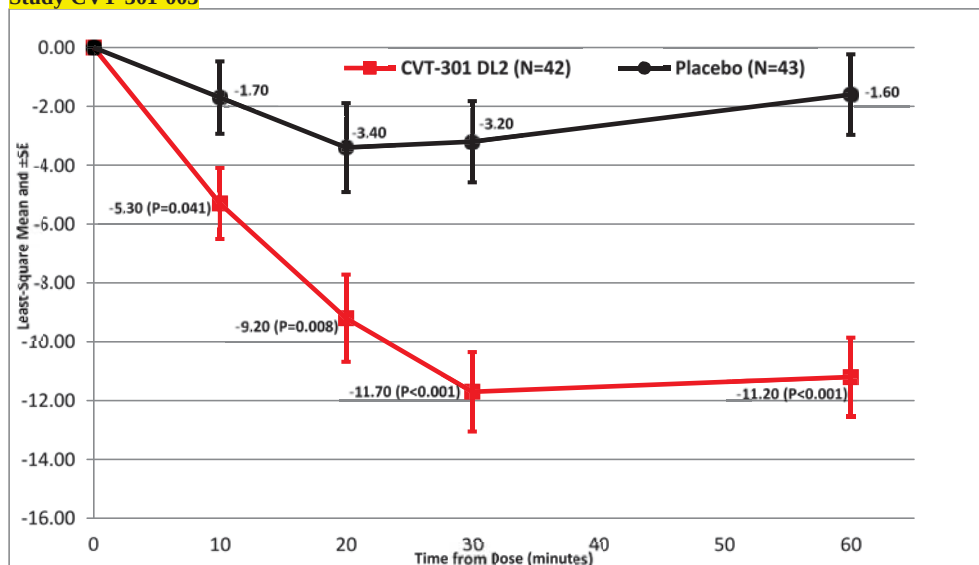
There was a statistically significant improvement in the UPDRS score mean change from pre-dose to 10-60 minutes post dose in the drug group compared to placebo.

EFFICACY RESULTS STUDY 003 COMPARED to 004.

The primary efficacy endpoint for the pivotal trial, CVT-301-004 was assessed at a single time point post dose, 30 minutes, at Week 12, while the primary efficacy endpoint for study CVT-301-003 was assessed over a one-hour time period (average post dose score 10-60 minutes) at Week 4. The applicant conducted an exploratory analysis of the change in UPDRS Part 3 scores for CVT 301 84 mg versus placebo at 30 minutes post dose. The results of these time measurements for Study CVT-301-003 and Study CVT-301-004 are depicted graphically below (Figures 9 and 10.)

Figure 9 The Comparison of the Change From Predose on the UPDRS Part 3 From 10 to 60 Minutes at Week 4 Study CVT-301-003

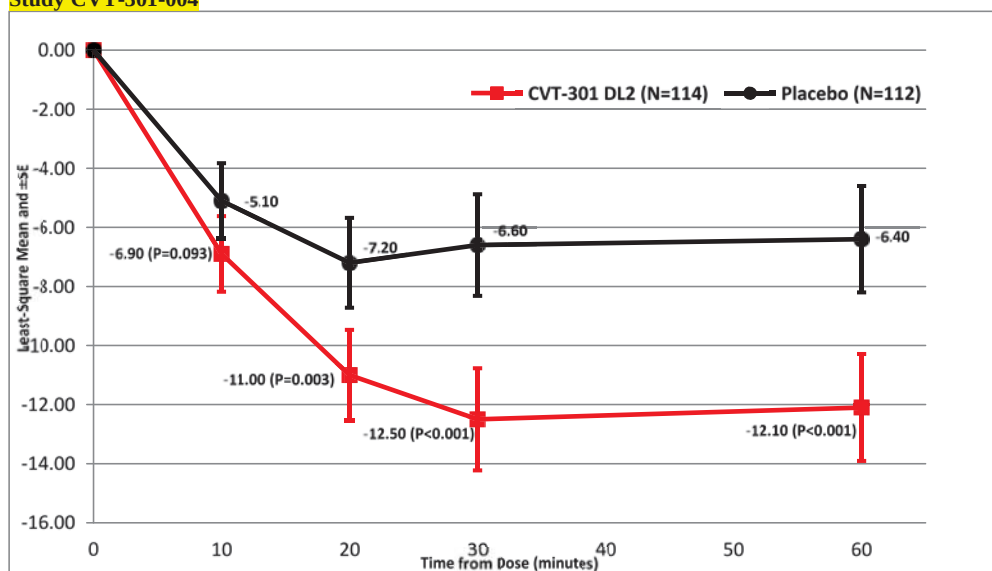
Study CVT-301-003



Source: Applicant

Figure 10 Comparison of the Change From Predose on the UPDRS Part 3 From 10 to 60 Minutes at Week 4 Study CVT-301-004

Study CVT-301-004



Source: Applicant

REVIEWER COMMENT:

The change in UPDRS part 3 score, post dose, was nominally significant at all time points in study CVT-301-003, while it was nominally significant at all time points except 10 minutes post dose in study CVT-301-004. Also, of note, there was a greater placebo response in the pivotal study CVT-301-004.

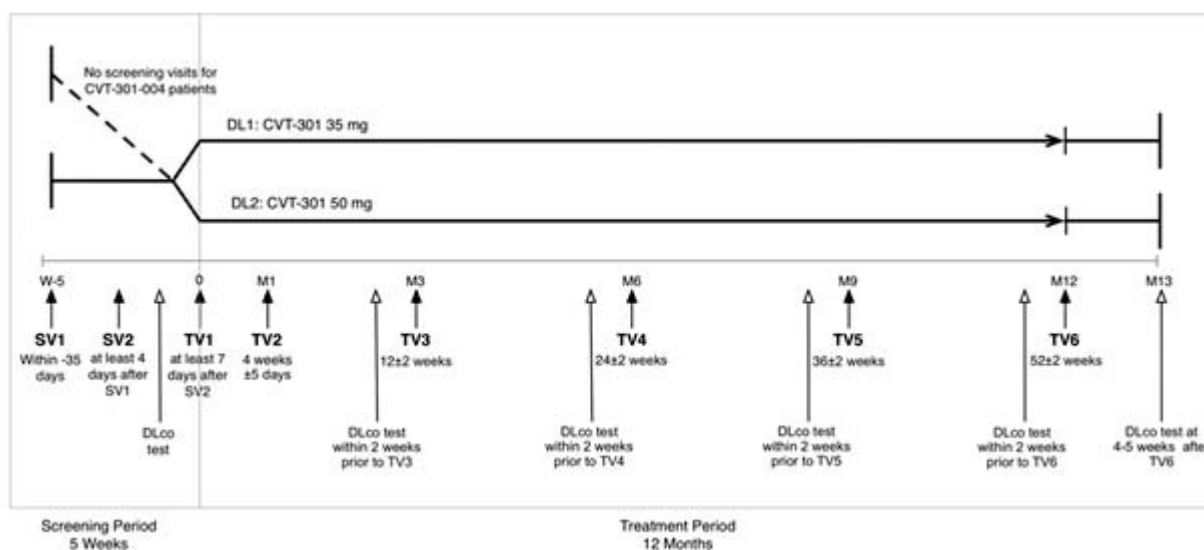
Study CVT-301-004E (Phase 3 Open Label Extension)

A 12 Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients with Motor Response Fluctuations OFF Phenomena

Study CVT-301-004E is 12-month, dose-level blinded, multicenter (North America and Europe) study investigating the safety and efficacy of 2 inhaled dose levels of CVT-301 (60 mg and 84 mg) in PD subjects experiencing motor response fluctuations (OFF phenomena).

The study design is depicted schematically in Figure 11.

Figure 11 Design Study CVT-301-004E



Abbreviations: DL1 = dose level 1 (60 mg, corresponding to 35 mg FPD); DL2 = dose level 2 (84 mg, corresponding to 50 mg FPD); DLco = carbon monoxide diffusing capacity; M = month; SV = Screening Visit; TV = treatment visit

Spirometry was performed on the same day as the DLco test. Source: Study CVT-301-004E CSR Figure 1

Source: Applicant

The study is an extension of Study CVT-301-004; however, CVT-301 naïve subjects, subjects randomized to the observational arm of Study CVT-301-005, and subjects

who previously completed Study CVT-301-003 and Study CVT-301-009 were also enrolled if they met Study CVT-301-004E eligibility criteria.

Subjects who received CVT-301 DL1 (60 mg) or DL2 (84) mg in Study CVT-301-004 remained on the same dose in Study CVT-301-004E. Subjects who received placebo in Study CVT-301-004, all former Study CVT-301-003 and Study CVT-301-009 subjects, as well as CVT-301 naïve subjects were randomized in 1:1 ratio to CVT-301 DL1 (60 mg) or DL2 (84) mg in Study CVT-301-004E. Randomization was stratified by the subject's Hoehn and Yahr stage (<2.5 versus ≥2.5) to balance the severity of disease across each treatment group and by screening spirometry (FEV1<60% or FEV1/FVC ratio <70% versus FEV1 ≥60% and FEV1/FVC ratio ≥70%). For the subjects who received placebo in CVT-301-004, the stratification of CVT-301-004 was used.

The first dose of inhaled CVT-301 in this study was administered in the clinic on Day 1 (TV 1) and the last scheduled dose at Study Week 52 ± 2 weeks (TV 6). In between clinic visits, subjects were to administer dose-level blinded study drug at home to treat up to 5 OFF periods per day, as closely as possible to the time when they began to experience OFF symptoms.

Efficacy was evaluated from both in-clinic and at-home assessments.

The primary endpoint was based on safety.

Secondary efficacy endpoints included:

- proportion of subjects achieving resolution of an OFF to an ON state within 60 minutes after administration of study drug in the clinic, maintaining the ON state at 60 minutes after administration of study drug (examiner subjective assessment)
- PGI-C improvement
- change from baseline in PD Diary
- change from pre-dose in PDQ-39 sub-scores and summary index score
- change from pre-dose in 9-Item Patient Health Questionnaire (PHQ-9) sum score
- change from baseline in UPDRS Part 2 score

Demographics

Overall, the demographic and baseline characteristics were comparable between treatment groups with no observed notable differences (Figure 12).

Figure 12 Demographic and Baseline Characteristics

Characteristic	Statistic	CVT-301 DL1	CVT-301 DL2	Total
Age (years)	n	153	159	312
	Mean (SD)	63.9 (8.76)	62.9 (8.34)	63.4 (8.55)
Age (years)				
<65	n (%)	71 (46.4)	80 (50.3)	151 (48.4)
≥65	n (%)	82 (53.6)	79 (49.7)	161 (51.6)
Gender				
Male	n (%)	110 (71.9)	119 (74.8)	229 (73.4)
Female	n (%)	43 (28.1)	40 (25.2)	83 (26.6)
Ethnicity				
Hispanic or Latino	n (%)	4 (2.6)	5 (3.1)	9 (2.9)
Not Hispanic or Latino	n (%)	149 (97.4)	154 (96.9)	303 (97.1)
Race				
American Indian or Alaska Native	n (%)	0	1 (0.6)	1 (0.3)
Asian	n (%)	1 (0.7)	5 (3.1)	6 (1.9)
Black or African American	n (%)	3 (2.0)	3 (1.9)	6 (1.9)
Native Hawaiian or other Pacific Islander	n (%)	1 (0.7)	0	1 (0.3)
White	n (%)	147 (96.1)	150 (94.3)	297 (95.2)
Unknown	n (%)	0	0	0
Other	n (%)	1 (0.7)	0	1 (0.3)
Height (cm)	n	153	159	312
	Mean (SD)	170.62 (9.002)	172.51 (9.524)	171.58 (9.305)
Weight (kg)	n	153	159	312
	Mean (SD)	80.66 (15.656)	82.45 (17.305)	81.57 (16.515)
BMI (kg/m ²) ^a	n	153	159	312
	Mean (SD)	27.65 (4.820)	27.59 (4.790)	27.62 (4.797)
Country				
Canada	n (%)	4 (2.6)	4 (2.5)	8 (2.6)
Czech Republic	n (%)	5 (3.3)	3 (1.9)	8 (2.6)
Poland	n (%)	39 (25.5)	45 (28.3)	84 (26.9)
Spain	n (%)	5 (3.3)	6 (3.8)	11 (3.5)
United States of America	n (%)	100 (65.4)	101 (63.5)	201 (64.4)

Characteristic	Statistic	CVT-301 DL1	CVT-301 DL2	Total
Smoking History				
Never	n (%)	103 (67.3)	99 (62.3)	202 (64.7)
Former	n (%)	48 (31.4)	51 (32.1)	99 (31.7)
Current	n (%)	2 (1.3)	9 (5.7)	11 (3.5)
MMSE Total Score	n	153	159	312
	Mean (SD)	28.8 (1.37)	29.1 (1.26)	28.9 (1.32)
Screening Spirometry				
FEV1 <60% or FEV1/FVC ratio <70%	n (%)	8 (5.2)	10 (6.3)	18 (5.8)
FEV1 ≥60% and FEV1/FVC ratio ≥70%	n (%)	145 (94.8)	149 (93.7)	294 (94.2)
Baseline PD Severity				
Hoehn & Yahr scale <2.5 points	n (%)	94 (61.4)	97 (61.0)	191 (61.2)
Hoehn & Yahr scale ≥2.5 points	n (%)	59 (38.6)	62 (39.0)	121 (38.8)

Abbreviations: BMI = body mass index; CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LD = levodopa; MMSE = Mini Mental State Examination; PD = Parkinson's disease; SD = standard deviation.

^a BMI was calculated as [weight (kg)] / [height (m)]².

Source: Table 14.1.3.1.1.

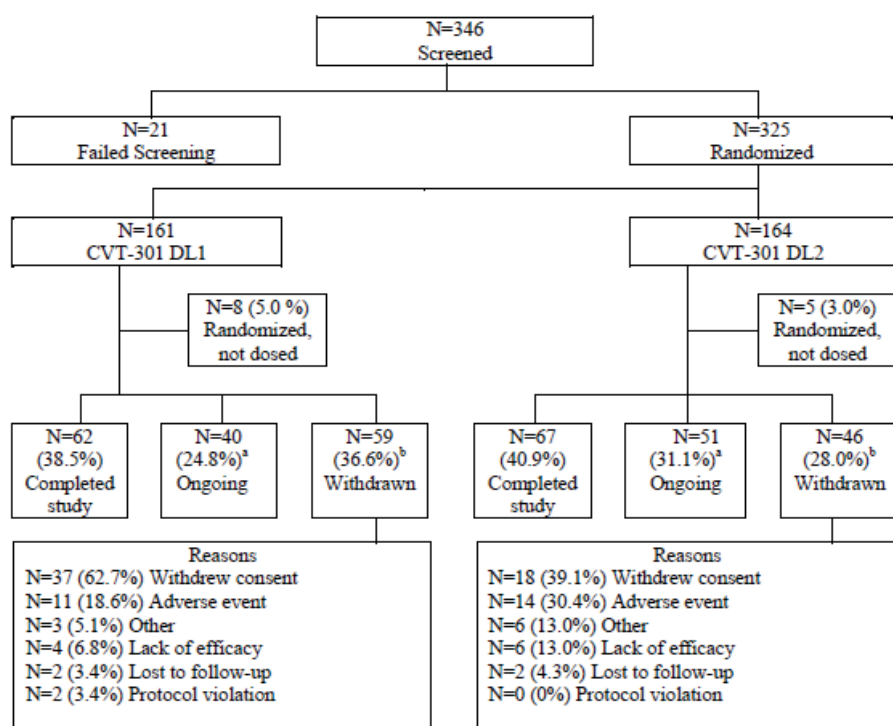
Source: Applicant

Disposition

The interim data snapshot for Study CVT-301-004E included all data through December 20, 2017. Of the 346 subjects that were screened for the study, 325

subjects (93.9%) were randomized and 312 subjects (96.0%) received at least 1 dose of study drug and were included in the safety population (Figure 13).

Figure 13 Disposition of Patients



Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa.

^a The number of ongoing patients was calculated as (randomized – completed – withdrawn).

^b Includes the number of 'randomized not dosed' patients.

Source: Table 14.1.1.1.

Source: Applicant

REVIEWER COMMENT:

161 subjects received DL1 (60mg), with 38.5% completing the study, 25% on going and 37% withdrawing (63% withdrew consent, 19% withdrew for an adverse event and 7% for lack of efficacy.) 164 subjects received DL2 (84mg) with 41% completing the study, 31% ongoing and 28% withdrawing (39% withdrew consent, 30% withdrew for an adverse event and 13% for lack of efficacy.)

Efficacy

The study is ongoing. Results from the last interim analysis (December 20, 2017) is presented for the proportion of subjects who achieved resolution of an OFF to an ON

within 60 minutes and maintained the ON at 60 minutes (responded: yes) with missing data imputed as a non-responder (Table 27.)

Table 27 Subjects Achieving Resolution of an OFF to an ON State within 60 Minutes by Treatment Group and Visit Worst Case Imputation (Study CVT-301-004E ITT Population)

Visit	CVT-301 60 mg (N = 144)		CVT-301 84 mg (N = 153)	
	n	Responder (yes), n (%)	n	Responder (yes), n (%)
TV2: Week 4	129	88 (68.2)	138	91 (65.9)
TV3: Week 12	120	79 (65.8)	132	83 (62.9)
TV4: Week 24	99	66 (66.7)	115	72 (62.6)
TV5: Week 36	69	35 (50.7)	83	53 (63.9)
TV6: Week 52	46	21 (45.7)	57	37 (64.9)

Abbreviations: ITT = intent-to-treat

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 subject is classified based on the available assessment. In case the assessment of maintenance of ON at 60 minutes is missing, the subject is classified as a non-responder. The missing values are counted as non-responder. Percentages are based the number of subjects at each visit.

Source: [Study CVT-301-004E CSR Table 14.2.1.1](#)

Source: Applicant

REVIEWER COMMENT:

The treatment blind in this study was incomplete (dose level) which may introduce bias. CVT-301 DL 2 (84 mg) and CVT-301 DL1 (60 mg) performed similarly from Week 4 to Week 24. At Weeks 36 and 52, CVT-301 DL 2 (84 mg) demonstrated greater numerical response than CVT-301 DL1 (60 mg.) Due to a decreasing sample size at successive visits, however, the significance of this difference is not conclusive.

SUMMARY OF EFFICACY

The efficacy results for the treatment of effect of CVT-301 for symptoms of OFF periods in patients with PD in the pivotal study CVT-301-004 is statistically significant for the primary endpoint, change in UPDRS part 3 score 30 minutes post dose at Week 12. Sensitivity analyses of the primary endpoint were very similar to that from the primary analysis (ie, statistically significant results for MMRM ANCOVA model based on overall ITT population), with the exception of the analysis with the addition of region by treatment interaction in the model, which resulted in p-values that were not statistically significant (p=0.094 for DL2), ; However, the number of patients randomized in the North American region was much larger than sites in the European region.

The phase 2b study CVT-301-003 assessed the same doses of CVT-301 as the pivotal study, however, the treatment effect used a different primary endpoint, change in the average post dose response of the UPDRS part 3 score (10- 60 minutes post dose) at Week 4. In addition, patients were titrated from 60mg (2 weeks) to 84mg (2 weeks.) A comparison of the results of the UPDRS part 3 score of the two studies at Week 4, at 10 minute intervals from 10 to 60 minutes post dose, revealed a similar magnitude of treatment effect.

The open label extension study, Study CVT-301-004E, is ongoing. The treatment effect as measured by responder rate of subjects achieving OFF to ON state 60 minutes post-dose is approximately 65%. However, the decrease in sample size (drop out) over time and that makes it difficult to interpret the clinical meaningfulness of these results.

7 Review of Safety

Safety Summary

7.1 Methods

The integrated safety data includes combined safety data from multiple-dose clinical studies conducted in PD subjects. Two multiple dose, placebo- controlled studies (CVT-301-003 and CVT-301-004) assessed the efficacy, safety and tolerability of the planned clinical doses in PD subjects. Two 12-month long-term safety Phase 3 studies (CVT-301-004E and CVT-301-005) provide the basis for the long-term safety of the planned clinical dose in PD subjects, with study CVT-301-005 providing long-term data from a randomized study versus a standard of care observational control cohort.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The analysis pools are defined below and shown in Table 28.

- **ISS Analysis Pool 1:** All Safety Population subjects in placebo-controlled multiple dose studies in PD subjects (**CVT-301-003 and CVT-301-004**).
- **ISS Analysis Pool 2:** All CVT-301-treated Safety Population subjects in uncontrolled or observational cohort controlled multiple dose studies in PD subjects (**CVT-301- 005 and CVT-301-004E**)
- **ISS Analysis Pool 3:** All CVT-301-treated Safety Population subjects in uncontrolled, placebo-controlled or observational cohort-controlled multiple-dose studies in PD subjects (**CVT-301-003, CVT-301-004, CVT-301-005 and CVT-301-004E**)

Table 28 Integrated Summary of Safety Analysis Pools

Study	Reason for exclusion from ISS analysis pools	ISS Analysis Pool 1	ISS Analysis Pool 2	ISS Analysis Pool 3
CVT-301-001	Study in healthy volunteers	-	-	-
CVT-301-002	Single dose study in PD subjects ^a	-	-	-
CVT-301-003	-	Included	-	Included
CVT-301-004	-	Included	-	Included
CVT-301-004E	-	-	Included	Included
CVT-301-005	-	-	Included	Included
CVT-301-006	Study in healthy volunteers	-	-	-
CVT-301-007	Study in healthy volunteers (smokers/nonsmokers)	-	-	-
CVT-301-008	Study in asthmatic adults	-	-	-
CVT-301-009	Single dose study in PD subjects ^b	-	-	-
CVT-301-010	Study in healthy volunteers	-	-	-

^aThe subjects received two single doses CVT-301 (one dose of 25 mg levodopa fine particle dose [FPD] and one dose of 50 mg levodopa FPD) and one single dose of placebo.

^bThe subjects received one single dose of CVT-301 or placebo immediately after the first morning dose of oral levodopa/carbidopa.

Abbreviation: PD = Parkinson's disease.

Source: Applicant

Of note, in Study CVT-301-004, which provides the primary support of effectiveness in the application, patients were randomized to either DL1 (60mg), DL2 (84mg) or placebo for a 12 week maintenance period. In Study CVT-301-003 patients were titrated from 60mg to 84mg without a washout period; patients remained on each dose for only 2 weeks. Although both studies are in POOL 1, the results of study CVT-301-004 provide the most interpretable information for adverse events at the to-be-marketed dose of 84mg (Table 29).

Table 29 Study CVT-301-004 Analysis Populations

STUDYID	ACTARM	Full Analys	Safety	ITT	Per-Protocol	Completer
CVT-301-004	CVT 301 DL1 (60)	113	113	113	97	96
	CVT 301 DL2 (84)	114	114	114	94	97
	Placebo	112	112	112	95	97

REVIEWER NOTE:

The Full Analysis set, Safety Population and Intention to Treat (ITT) populations were identical for Study CVT-301-004.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of the interim database snapshot date of December 20, 2017, 1103 subjects were enrolled in the CVT-301 program, including 951 subjects with PD. This calculation accounts for all subjects participating in more than 1 study and does not count them multiple times. A total of 897 subjects received at least 1 dose of CVT-301 across all studies, including 754 subjects with PD (Table 30).

Table 30 CVT-301 Estimated Total Subject Exposure in the Clinical Program

Study (Phase)	Population	Number of Subject	Number of Subjects Exposed	Levodopa FPD (mg)	Route and Duration of Treatment
Clinical Pharmacology and Special Populations Studies					
CVT-301-001 (Phase 1)	Healthy Volunteers	26	26	10, 20, 30, 40, 50	Inhalation Single dose
CVT-301-006 (Phase 1)	Healthy Volunteers	13	12	50, 70, 105	Inhalation Single dose
CVT-301-007 (Phase 1)	Smokers / Non-smokers	63	56	50	Inhalation Single dose
CVT-301-008 (Phase 1)	Asthmatic Adults	26	25	50	Inhalation 3 doses in 1
CVT-301-010 (Phase 1)	Healthy Volunteers	24	24	35, 50	Inhalation Single dose
Total CVT-301 Exposure in Clinical Pharmacology Studies			143		

Parkinson's Disease Patient Studies					
CVT-301-009 (Phase 1)	PD Patients	36	36	50	Inhalation Single
CVT-301-002 (Phase 2a)	PD Patients	24	24	25 and 50	Inhalation 2 doses
CVT-301-003 (Phase 2b)	PD Patients	89	43	35 and 50	Inhalation 4 weeks
CVT-301-004 (Phase 3)	PD Patients	351	227	35 or 50	Inhalation 12 weeks
CVT-301-004E ^a (Phase 3)	PD Patients	325	153 ^b	35 or 50	Inhalation 12
CVT-301-005 (Phase 3)	PD Patients	408	271 ^c	50	Inhalation 12
Total CVT-301 Exposure in PD subjects			754		
Total CVT-301 Exposure in all subjects			897		

^a 12-month extension study to CVT-301-004.

^b Calculated number of subjects treated with CVT-301 in Study CVT-301-004E excluding those rollover subjects previously treated with CVT-301, from Studies CVT-301-003/009 (15 subjects) and CVT-301-004 (144 subjects).

^c Calculated number of subjects in CVT-301-005 including rollover subjects from CVT-301-002 and CVT-301-003. Abbreviations: FPD = fine particle dose; PD = Parkinson's disease.

Source: Applicant

At the higher dose level of 84 mg, 365 PD subjects were treated for ≥ 6 months, , and 307 PD subjects were treated for ≥ 12 months (Table 31).

**Table 31 Exposure to Study Treatment by Dose Level (Safety Population)
as of the Interim Database Snapshot Date of 20 December 2017**

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270	Placebo N=155	CVT-301 N=583	CVT-301 N=705
Exposure to study treatment, categorical, ^a DL1 (60 mg), n (%)				
N	156	0	153	237
< 3 months	58 (37.2)		24 (15.7)	66 (27.8)
≥ 3 months	98 (62.8)		129 (84.3)	171 (72.2)
≥ 6 months			119 (77.8)	122 (51.5)
≥ 9 months			107 (69.9)	111 (46.8)
≥ 12 months			81 (52.9)	85 (35.9)
Exposure to study treatment, categorical, ^a DL2 (84 mg), n (%)				

N	154	430	508
< 3 months	55 (35.3)	38 (8.8)	90 (17.6)
≥ 3 months	99 (63.5)	392 (91.2)	418 (82.0)
≥ 6 months		359 (83.5)	365 (71.6)
≥ 9 months		339 (78.8)	339 (66.5)
≥ 12 months		302 (70.2)	307 (60.2)

Source: CDTL

REVIEWER COMMENT:

The to-be-marketed dose is 84mg, DL2. 369 subjects have been exposed for >6months and 307 subjects for >12 months, meeting the regulatory requirements for approval.

7.2.2 Explorations for Dose Response

Subjects were allowed to use CVT-301 for the treatment of the symptoms of OFF episodes up to 5 times a day. Table 32 below shows the proportion of subjects using the study treatment (number of doses per day at least once) and the proportion of days with number of doses administered.

Table 32 Exposure to Study Treatment (Safety Population) as of the Interim Database Snapshot Date of 20 December 2017

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270	Placebo N=155	CVT-301 N=583	CVT-301 N=705
Proportion of subjects using the doses per day at least once, n (%)				
0 doses	207 (76.7)	117 (75.5)	492 (84.4)	595 (84.4)
1 doses	265 (98.1)	149 (96.1)	565 (96.9)	688 (97.6)
2 doses	247 (91.5)	139 (89.7)	544 (93.3)	655 (92.9)
3 doses	207 (76.7)	128 (82.6)	483 (82.8)	584 (82.8)
4 doses	120 (44.4)	70 (45.2)	355 (60.9)	412 (58.4)
5 doses	52 (19.3)	20 (12.9)	168 (28.8)	198 (28.1)
>5 doses	11 (4.1)	8 (5.2)	56 (9.6)	62 (8.8)
Proportion of days ^b with number of doses administered				

0 doses	3835 (20.1)	1780 (17.7)	30821 (18.0)	34656 (18.2)
1 doses	5133 (26.8)	2680 (26.6)	40362 (23.6)	45495 (23.9)
2 doses	4895 (25.6)	2613 (25.9)	40075 (23.4)	44970 (23.6)
3 doses	3456 (18.1)	2088 (20.7)	37797 (22.1)	41253 (21.7)
4 doses	1338 (7.0)	795 (7.9)	17156 (10.0)	18494 (9.7)
5 doses	421 (2.2)	109 (1.1)	4830 (2.8)	5251 (2.8)
>5 doses	43 (0.2)	8 (0.1)	172 (0.1)	215 (0.1)

Source: Applicant

The total number of patients who used at least 5 doses per day of CVT-301 (DL1 or DL2) is presented by day (interval) Table 33.

Table 33 Total Number of Patients who used at Least 5 Doses per Day (Interval)

Dose Categories*	Months of Exposure**	N=469***
DL1 (60mg)		
≥ 5 Doses per Day (Treated Consecutively)	≥3 to <6 months	4
	≥6 months to <12	0
	≥12 months	1
DL2 (84mg)		
≥ 5 Doses per Day (Treated Non-	≥3 to <6 months	13
	≥6 months to <12	4
	≥12 months	2

NOTE: Studies CVT-301-004, 004e and 005 were included in this analysis.

* Consecutive refers to subjects who took ≥5 doses on each day of the exposure period with no days off from that dosing. Non-consecutive exposure is the sum of all days during the study in which subjects took ≥5 doses per day.

**3 months = 12 weeks +/- 2 weeks or 70 days; 6 months= 24 weeks +/-2 weeks or 154 days; 12 months = 52 weeks +/- 2 weeks or 350 days.

***Number of subjects taking at least one dose of DL2 (84mg).

Source: CDTL

REVIEWER COMMENT:

The majority of subjects (POOL 3) used between 1 and 3 doses per day. Thirteen patients used ≥ 5 doses per day for at least 30-179days.

7.3 Major Safety Results

7.3.1 Deaths

Two fatal AEs were reported in clinical trials of CVT-301. One subject in Study CVT-301-004 died of completed suicide (Study CVT-301-004), and 1 subject in CVT-301-005 died of anoxia subsequent to drowning (Study CVT-301-005). Both deaths were considered by the investigators to be definitely not related to study treatment. (Table 34)

Table 34 Fatal Treatment-emergent Adverse Events in CVT-301 Clinical Studies

Study Identifier	Unique Subject	Reported Term/	Causality (investigator assessment)	Study start day/end	Days from last
CVT-301-004	CVT-301-004- (b) (6)	Completed Suicide/ Completed Suicide	Definitely Not Related	14/14	13
CVT-301-005	CVT-301-005- (b) (6)	Hypoxic/Anoxic Encephalopathy/ Hypoxic-Ischaemic Encephalopathy ^a	Definitely Not Related	45/49	3

Narratives for the two deaths are provided below.

Subject (b) (6) was a 66 year old White male with a history of PD (diagnosed (b) (6)) with motor fluctuations. Concomitant medications included carbidopa levodopa and Tizanidine. The subject took first dose of CVT-301 35mg on (b) (6). The last reported dose was at TV1 clinic visit. On (b) (6) the subject committed suicide by jumping off the balcony of his apartment. All Columbia-Suicide Severity Rating Scale (C-SSRS) assessments were reviewed and showed that the subject had never reported any suicidal thoughts or behaviors. An autopsy was performed but results were not provided.

Subject (b) (6) was a 73-year-old White male with a history of PD diagnosed in (b) (6) with motor fluctuations. His medical history was significant for allergy to penicillin, cephalosporin, ciprofloxacin and mirabegron. He has osteoarthritis, atrial flutter, nephrolithiasis, hyperlipidemia, hypertension, insomnia, neurogenic bladder, kyphoscoliosis, urinary incontinence, chronic kidney disease, memory problems, depression and constipation. His surgical history included bilateral knee replacement, right ankle surgery, s/p repair inguinal hernia and lithotripsy. The subject had a history of smoking from age 14 to 16 years old, approximately 20 cigarettes a day.

His concomitant medications included carbidopa levodopa, entacapone, fenofibrate, Lisinopril, clonazepam and polyethylene glycol.

He took his first dose of CVT-301 50mg on (b) (6) and continued on this dose through (b) (6).

On (b) (6) an SAE of hypoxic/anoxic encephalopathy was reported. The subject had been using his home pool and was found face down in the pool. He was admitted to the hospital and placed on 'life support'. On (b) (6) he was removed from life support and died the same day.

Of note, the subject was noncompliant with the investigational product; he accidentally discarded 14 capsules from the kit (#22272) at TV2.

In addition, the subject was noted to have changes in pulmonary function test results at one-time point.

On (b) (6) (TV2), spirometry results, performed at the study site, showed changes from Baseline; FEV1 was -23.2% changed from Baseline and FVC was -18.8% changed from Baseline. However, FEV1/FVC ratio was only -5.7% change from Baseline. No other reported, FEV1, FVC, FEV1/FVC ratio or DLCO value evaluated met any pulmonary function test potential interest criterion.

REVIEWER COMMENT:

There were two deaths; one death during the double-blind, placebo-controlled trial CVT-301-004 and one death in the long term study, CVT-301-005. The subject in the double blind placebo controlled study, CVT-301-0004 on DL1 (60mg), committed suicide. The second subject in the long term safety study, CVT-301-005, on DL2 (84mg), drowned (hypoxic/anoxic encephalopathy.) Of note, the subject in the long term safety study was noted to have had a change in pulmonary function tests, 10 days prior to the incident. There was a -23.2% change in FEV1, -18.8% change in FVC, and FEV1/FVC ratio change of -5.7%. There was no significant history of pulmonary disease except for remote history of smoking, which is unlikely related to the cause of death.

7.3.2 Nonfatal Serious Adverse Events

There were 13 SAEs in POOL 1; 3 in placebo treated cohort, 7 in DL1 cohort, and 3 in DL2 cohort. All but one SAE (CVT-301-003, placebo) occurred in the pivotal study CVT-301-004.

Serious adverse events (SAEs) for the double-blind placebo controlled trials are presented in the Table 35 below:

Table 35 Serious Adverse Events for Double Blind Placebo Controlled Studies (POOL 1)

Patient Number (USUBID)	Preferred Term	Study Day	Outcome
Placebo			
CVT-301-003-(b) (6)	Acute pancreatitis	71	resolved
CVT-301-004-(b) (6)	Lumbar spinal stenosis	70	Resolved
CVT-301-004-(b) (6)	Coronary artery disease	59	Resolved
DL1			
CVT-301-004-(b) (6)	Pericarditis	79	resolved
CVT-301-004-(b) (6)	Atrial fibrillation, bradycardia, chest pain, hypokalemia, syncope, renal failure, hypotension	44	resolved
CVT-301-004-(b) (6)	Chest pain, headache	77	resolved
CVT-301-004-(b) (6)	cholelithiasis	-19	resolved
CVT-301-004-(b) (6)	Completed suicide	14	fatal
CVT-301-004-(b) (6)	Intestinal obstruction	86	resolved
CVT-301-004-(b) (6)	Ischemic stroke	87	resolved
DL2			
CVT-301-004-(b) (6)	Syncope	-17	resolved
CVT-301-004-(b) (6)	Atrial fibrillation	41	Resolved
CVT-301-004-(b) (6)	Intervertebral disc protrusion, lumbar spinal stenosis	71	Resolved with sequelae

Source: Reviewer

The narrative summaries for each of the SAEs, for subjects on active study treatment (DL1 and DL2), are provided below.

DL1**Narrative:**

Subject (b) (6) was a 68-year-old White (not Hispanic or Latino) woman with a history of Parkinson's disease (b) (6) with motor response fluctuations

(OFF Phenomena) since (b) (6)

Medical history for this subject included heart attack, congestive heart failure, hypertension, atrial fibrillation, diabetes type II, menopause, environmental allergies, bilateral glaucoma, cholecystitis, rheumatoid arthritis, pneumonia, and L4-L5 spinal fusion. Surgical history included multiple coronary stent insertions, cholecystectomy, right shoulder rotator cuff surgery, left shoulder cyst removal, and benign cyst removed L4-L5.

Concomitant and prior medication for Parkinson's disease included carbidopa and levodopa 25/100, and selegiline. Other concomitant medications included Aspirin (acetylsalicylic acid), methotrexate, Sulindac (clinoril), Coreg (carvedilol), Plavix (clopidogrel), omeprazole, prednisone, montelukast, Xalatan (latanoprost), magnesium, folic acid, zinc, lisinopril, saline, fluticasone, lantus, Protonix (pantoprazole), Imdur (isosorbide mononitrate), Claritin (loratadine), magnesium, and heparin.

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6)
The subject continued to take CVT-301 35 mg through (b) (6)

On (b) (6) an SAE of pericarditis and an AE of fever were reported. The subject had been seen in an emergency room (ER) on (b) (6) for fever (reported to have been up to 101 degrees Fahrenheit) chest pain, abdominal pain, neck and back pain, and had been instructed to follow-up with her primary care physician (PCP). On (b) (6) the subject arrived in the ER after having visited an urgent care site the same date. Triage vital signs included oral temperature of 98.6° F, pulse oximetry (SpO2) of 96% on room air, respiratory rate of 16 breaths per minute (br/min), heart rate of 101.

The SAE of pericarditis and the AE of fever were resolved on (b) (6)
No additional adverse events were reported during this subject's participation in the study. The last dose of CVT-301 35 mg was on (b) (6) The subject completed the study and her last day in the study was on (b) (6)

Narrative:

Subject (b) (6) was a 72-year-old White (not Hispanic or Latino) man with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6)

Medical history for this subject included chest pain, atrial fibrillation, aortic aneurysm, hypertension, constipation, benign prostatic hyperplasia, hypercholesterolemia, back pain, restless leg syndrome, anxiety, fatigue, depression, shortness of breath, and allergy to codeine. Surgical history included aortic valve replacement, coronary heart bypass × 2 vessels, neck vertebra surgery, laminectomy, left hip replacement, and carotid artery surgery.

Concomitant medications included carbidopa and levodopa, atorvastatin, aspirin (acetylsalicylic acid), clonazepam, hydrocodone and acetaminophen, folic acid (supplement), vitamin B12 (supplement), gabapentin, sotalol, warfarin, sertraline, tamulosin, buspirone, tramadol, acetaminophen and codeine, fish oil (supplement), lisinopril/HCTZ (lisinopril and hydrochlorothiazide), diltiazem,

sodium chloride (infusion supplement), nitroglycerin, and lisinopril.

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6).
The subject continued to take CVT-301 35 mg through (b) (6).

On (b) (6) SAEs of chest pain, hypokalemia, and atrial fibrillation were reported. The subject's atrial fibrillation had been previously controlled with concomitant medications.

The subject went to the emergency room (ER) and was found to be in rapid atrial fibrillation when he arrived. He was admitted to the hospital on (b) (6) and treated with nitroglycerine 0.4 mg orally, aspirin 324 mg orally, and Cardizem drip (also reported as diltiazem 4 mL and sodium chloride 1000 mL intravenously). It was noted that the subject's chest pain was associated with the atrial fibrillation with RVR and that his symptoms had improved markedly on the Cardizem drip.

The SAE of hypokalemia resolved on (b) (6) and the SAEs of chest pain and atrial fibrillation resolved on (b) (6). The subject was discharged from the hospital on (b) (6).

Study drug was interrupted because of these events.

On (b) (6) the following 4 SAEs were reported: bradycardia, hypotension, renal failure, and syncope. On this date, the subject visited his primary care physician, who sent him to the ER because of hypotension with a blood pressure of 80/40 mm Hg. Hospital admission records note that syncope was secondary to symptomatic bradycardia and hypotension, and acute renal failure was secondary to dehydration. Treatment was provided with intravenous fluids (sodium chloride 1000 mL IV) and discontinuation of lisinopril/hydrochlorothiazide. In addition, treatment with sotalol was withheld.

The SAE of syncope was resolved on (b) (6). The SAEs of bradycardia, hypotension, and renal failure were all resolved on (b) (6). The subject was discharged from the hospital on this date.

The last dose of CVT-301 35 mg was taken on (b) (6).

The subject completed the study and his last day in the study was (b) (6).

Narrative:

Subject (b) (6) was a 66-year-old White (not Hispanic or Latino) man with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6).

Medical history for this subject included hypertension, coronary artery disease, claudication, stable pectoris angina, hypercholesterolemia, Grade 1 gastric lymphoma, gallstones, kidney stones, diverticulosis and diverticulitis, esophageal stricture, right ankle fracture, back pain, right wrist fracture, shoulder pain, osteoarthritis of the right knee and chest, gout right foot big toe, headaches, nausea, insomnia, mild anxiety, hydrochlorothiazide allergy, and levofloxacin allergy. Surgical history included stent placements, coronary artery bypass, cholecystectomy, large bowel resection, right rotator cuff surgery, right ankle surgery, esophageal dilation procedure, bilateral knee arthroscopy, and right hip

replacement.

Concomitant medications included Sinemet (carbidopa and levodopa), atenolol, lorazepam, dexamethasone, ibuprofen, indomethacin, isosorbide mononitrate, lisinopril, clopidogrel, omeprazole, nifedipine, vitamin B12 (supplement), Bactrim (sulfamethoxazole and trimethoprim), hydromorphone, and ondansetron.

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6). The subject continued to take CVT-301 35 mg through (b) (6). The last dose of study drug prior to the events was on (b) (6).

On (b) (6) SAEs of chest pain (chest pain) and headache (headache) were reported. On this date, the subject presented to the emergency department with a 2 day history of persistent midsternal chest pain without nausea, vomiting, diaphoresis, shortness of breath, or dyspnea after swimming.

Serial electrocardiograms (ECGs) showed sinus rhythm with occasional premature ventricular contractions (PVCs). Cardiac markers, including troponin I, brain natriuretic peptide, creatine kinase (CK), and CK-MB, were within normal limits and did not indicate any acute coronary event. Chest x-ray and brain computed tomography (CT) scan results were normal.

Treatment was provided with Dilaudid (hydromorphone) and aspirin in the emergency department for the SAEs. The subject was discharged from the hospital on (b) (6).

Study drug dose was not changed because of these events. The SAEs of chest pain and headache were resolved on (b) (6).

Narrative:

Subject (b) (6) was a 69-year-old White (not Hispanic or Latino) woman with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6).

Medical history for this subject included mild dementia, psoriasis (back of neck), high cholesterol (diet controlled), hip and left knee osteoarthritis, osteoporosis, muscle weakness of right eye, insomnia, hypersomnia, sleep apnea, Rytary (carbidopa and levodopa) intolerance, right and left cataracts, benign brain tumor (noncancerous meningioma), metatarsal fracture (left foot), acute appendicitis, and alcohol intolerance. Surgical history included right and left cataract removal, appendectomy, benign brain tumor removal, right eye surgery for muscle weakness, and tubal ligation.

Concomitant medications included Rytary (carbidopa and levodopa), pramipexole, and entacapone and zolpidem.

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6). The subject continued to take CVT-301 35 mg through (b) (6).

On (b) (6) during the screening period of the study, an SAE of cholelithiasis was reported. On this date, the subject was hospitalized due to abdominal pain. Gallstones were discovered and the subject was diagnosed with cholelithiasis. On

(b) (6) the subject underwent a cholecystectomy due to stoppage/blockage of the gallbladder. The subject was discharged from the hospital on May 7, 2016 with a prescription for Norco (hydrocodone-acetaminophen) as needed for pain, instructions to follow a low fat diet, and scheduled follow-up.

The last dose of CVT-301 35 mg was taken on (b) (6)

The subject completed the study and her last day in the study was (b) (6)

Narrative:

Subject (b) (6) was a 66-year-old White (Hispanic or Latino) male with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6) Full narrative under **DEATHS**

Narrative:

Subject (b) (6) was a 64-year-old White (not Hispanic or Latino) man with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6)

Medical history for this subject included gastric reflux, infrequent fecal incontinence, mild constipation, infrequent urinary incontinence, muscular pain, insomnia, anxiety, decreased olfaction, rapid eye movement sleep behavior disorder, elevated cholesterol, and macular degeneration. Surgical history included appendectomy.

Concomitant medications included entacapone, pramipexole, rasagiline, and Sinemet CR 50/200 (carbidopa and levodopa), acetaminophen, atorvastatin, citalopram, dexlansoprazole, gabapentin, lorazepam, and trazodone.

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6)

The subject continued to take CVT-301 35 mg through (b) (6)

On (b) (6) the subject experienced nausea and vomiting during the night. On (b) (6) an SAE of intestinal subocclusion was reported. The subject presented to the hospital on this date and subsequently was admitted with a diagnosis of intestinal subocclusion (large intestine, probably due to adhesions). Treatment included insertion of a nasogastric tube, nothing by mouth status for approximately 30 hours, dextrose intravenous infusions, and reduction of levodopa dosage (administered via nasogastric tube). Clinical improvement was observed after 24 hours of medical treatment and the event reportedly stopped after 48 hours. The subject was discharged home from the hospital on (b) (6) on his usual medications. Study drug was interrupted because of this event.

The SAE of intestinal subocclusion resolved on (b) (6)

The last dose of CVT-301 35 mg was taken on (b) (6)

The subject completed the study and his last day in the study was (b) (6)

Narrative:

Subject (b) (6) was a 61-year-old White (not Hispanic or Latino) man with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6)

Medical history for this subject included depression, allergy to salicylates (per the MedWatch form), and spondylosis of the LS spine.

Concomitant medications included Madopar (carbidopa and benserazide), Sinemet CR (carbidopa and levodopa), Akineton (biperiden), ReQuip Modutab (ropinirole), Asentra (sertraline), and Actilyse (alteplase).

The subject took the first dose of inhaled CVT-301 35 mg on (b) (6)

The subject continued to take CVT-301 35 mg through (b) (6)

On (b) (6) while the subject was in screening period for the CVT-301-004E extension study, an SAE of right hemisphere ischaemic stroke (ischaemic stroke) was reported and the subject was admitted to the hospital. Hospital diagnoses included cerebral infarction caused by blockage of cerebral arteries and subsiding left hemiparesis. A CT of the head performed in the emergency department showed no characteristics of intracranial bleeding. There was a discrete blurring of the cortico subcortical border in the right frontal area, and suspicion of a vascular change. On (b) (6) the subject was discharged from the hospital in stable general condition. Recommendations at discharge included follow ups in the neurology and cardiology clinics, dietary restriction of polyunsaturated fats, and discharge medications. The subject was to be admitted to the neuro rehabilitation department on (b) (6) (due to the sequelae of persistent left hemiparesis).

Study drug dose was not changed because of the SAE for the CVT-301-004 study as the subject had just taken his final study drug dose that day. But subsequently, the subject was discontinued from the CVT-301-004E study due to the SAE. He had not yet been administered any study drug for the extension study.

The SAE was considered resolved with sequelae on (b) (6)

The subject completed the CVT-301-004 study and his last day was (b) (6)
(b) (6)

DL2**Narrative:**

Subject (b) (6) was a 63-year-old White (not Hispanic or Latino) female

with a history of Parkinson's disease (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6)

Medical history for this subject included Barrett's esophagus, chest pain, depression, anxiety, nausea, insomnia, chronic pancreatic insufficiency, gastroparesis, hypothyroidism, headaches, allergy to codeine, and allergy to Reglan (metoclopramide). Surgical history included hysterectomy and cholecystectomy.

Concomitant medications included Neupro (rotigotine), carbidopa and levodopa, and carbidopa, Creon (pancreatin), estradiol, Levoxyl (levothyroxine), butalbital, Zofran (ondansetron), hydrocodone/APAP, and Lopamidol (iopamidol).

The subject had not yet received the first dose of inhaled CVT-301 50 mg at the time of the events.

On (b) (6) an SAE of syncope was reported. Five days earlier, on (b) (6) (b) (6) the subject started coughing and on (b) (6) the subject's primary care physician prescribed Ceftin for an upper respiratory infection. On the morning of (b) (6), the subject developed a headache, dry heaves, and reported having one event of forceful vomit. She went to the emergency room (ER) and while in the waiting room, the subject became weak and experienced a syncopal event. Vital signs at 11:59 included: pulse oximeter 100% on room air, blood pressure 158/83 mm Hg, temperature 36.7°C, pulse rate 90 beats per minute, and respirations 12 breaths per minute. At 15:06, vital signs were pulse oximeter 98% on room air, blood pressure 116/64 mm Hg, pulse 70 bpm, respirations 18 bpm, and temperature 36.7°C. The subject was admitted to the hospital on (b) (6) and treated with Zofran, hydrocodone/APAP, and fluids. Upon physical examination, the subject's skin was abnormal in color, with diaphoresis, and pallor. Computerized tomography of the brain without contrast performed that day revealed polypoid sinusitis. The subject felt better and was discharged from the hospital on (b) (6)

This SAE was resolved on (b) (6)

The subject took the first dose of inhaled CVT-301 50 mg on (b) (6) The subject continued to take CVT-301 50 mg through (b) (6)

The subject completed the study and her last day in the study was (b) (6)

Narrative:

Subject (b) (6) as a 73-year-old White (not Hispanic or Latino) woman with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6)

Medical history for this subject included thrombocytopenia/immune thrombocytopenic purpura, hypertension, hyperlipidemia, osteoarthritis,

gastroesophageal reflux disease, ulcerative colitis, stomach ulcers, hiatal hernia, polyps in colon, constipation, chronic rhinitis, bout of atrial fibrillation, bilateral knee arthritis, anemia, sleep disturbances, menopause, and dry eye. Surgical history included right hip replacement and right knee replacement.

Concomitant medications included entacapone, Azilect (rasagiline), Sinemet (carbidopa and levodopa), Mirapex (pramipexole), and beta carotene, clonazepam, losartan, amlodipine, labetalol, omeprazole, vitamin B12 (for gastroesophageal reflux disease), iron supplement (for anemia), Restasis (cyclosporine), red yeast rice, Premarin (estrogens conjugated), and MiraLax (polyethylene glycol 3350).

The subject took the first dose of inhaled CVT-301 50 mg on (b) (6). The subject continued to take CVT-301 50 mg through (b) (6). The last dose of study drug prior to the SAE was received on (b) (6) at 03:40 pm.

On (b) (6) an SAE of atrial fibrillation (atrial fibrillation) was reported. The subject was admitted to the hospital on the same day with a diagnosis of persistent atrial fibrillation. Treatment was provided with a Cardizem (diltiazem) drip.

The SAE of atrial fibrillation was resolved on (b) (6) the subject was discharged from the hospital on this date in good condition with instructions to follow a low sodium diet and to perform activity as tolerated. Discharge diagnoses included atrial fibrillation, thrombocytopenia, and hypertension. Study drug dose was not changed because of this event.

The last dose of CVT-301 50 mg was taken on (b) (6). The subject completed the study and her last day in the study was (b) (6).

Narrative:

Subject (b) (6) was a 61-year-old White (not Hispanic or Latino) man with a history of Parkinson's disease (since (b) (6) with motor response fluctuations (OFF Phenomena) since (b) (6).

Medical history for this subject included inguinal hernia, hypertension, multilevel discopathy of the lumbar spine, and spinal pain syndrome. Surgical history included appendectomy and right shoulder surgery.

Concomitant medications included rasagiline, Mydocalm (tolperisone), Madopar and Madopar HBS (levodopa and benzaseride), Viregyt K (amantadine), and Nakom (carbidopa and levodopa), Bisocard (bisoprolol), Celebrex (celecoxib), Agen (amlodipine), Anestoloc (pantoprazole), Vigantoletten (vitamin D3 supplement, for prevention of vitamin D3 deficiency), calcium supplement (for prevention of calcium deficiency), Ketonal (ketoprofen), Dexaven (dexamethasone), and Pyralginum (metamizole).

The subject took the first dose of inhaled CVT-301 50 mg on (b) (6). The subject continued to take CVT-301 50 mg through (b) (6).

On (b) (6) SAEs of spinal stenosis lumbar (lumbar spinal stenosis) and

herniated disc on L4/L5 level (intervertebral disc protrusion) were reported. The subject was admitted to the neurology ward of the hospital on this date due to strong pain in the LS section of the spine radiating to both lower extremities. Prior to this exacerbation, he was able to walk independently with the aid of a stick. On (b) (6) an x-ray of the lumbar sacral section of the spine showed right sided scoliosis, loss of physiological lordosis, intervertebral disc stenosis L4/L5 and L5/S, posterior instability at L3/L4 and L5/S1 level, and the height of the vertebral bodies was maintained.

On (b) (6) an MRI scan of the LS section of the spine was performed with the following results: there was a minor degree of L4 disc slippage; intervertebral disc dehydration was present at all levels; centralized herniation of the intervertebral disc at L4/L5 level.

On (b) (6) he was admitted to the neurosurgery clinic. On (b) (6) the subject underwent lumbar stenosis surgery which included spinal canal decompression at L4/L5 level, PLIF stabilization, and transpedicular MIDLF L4/L5. The subject's condition improved after surgery, and he was able to independently stand at the bedside.

On (b) (6) the subject was discharged from the neurosurgery clinic and admitted back to the neurology ward to undergo further treatment and physical rehabilitation.

Study drug dose was not changed because of these events, but because the subject was hospitalized and unable to complete Treatment Visit 4, he terminated the study early. The SAEs of spinal stenosis lumbar and herniated disc on L4/L5 level were resolved with sequelae on (b) (6)

The last dose of CVT-301 50 mg was taken on (b) (6) The subject's last day in the study was on (b) (6)

REVIEWER COMMENT:

The majority of SAEs in double blind placebo-controlled studies occurred in subjects in DL1 (60mg) treatment group. The SAEs are most likely related to the subjects' age and underlying disease (Parkinson's disease.)

7.3.3 Dropouts and/or Discontinuations

Study CVT-301-004

In the pivotal Phase 3 study, **CVT-301-004** the reason for discontinuation of patients is presented in the table below (Table 36).

Table 36 Subject Reason for Discontinuation, Study CVT-301-004

Reason for Discontinuation/Withdrawal	CVT 301 DL1 N=113(%)	CVT 301 DL2 N=114(%)	Placebo N=112 (%)	All N=339 (%)
Adverse event	3 (3)	6(5)	3(3)	12(4)
Lack of efficacy	1(1)	1(1)	0(0)	2(1)
Lost to follow-up	2(2)	0(0)	0(0)	2(1)
Other	2(2)	1(1)	2(2)	5(1)
Withdrawal by subject	9(8)	9(8)	10(9)	28(8)
All	17(15)	17(15)	15(13)	49(14)
Reason SAE				
Coughing	0(0)	1(1)	0(0)	1(0)
Drug inhalation triggered cough	0(0)	1(1)	0(0)	1(0)
Dry throat	0(0)	1(1)	0(0)	1(0)
Hip fracture	0(0)	0(0)	1(1)	1(0)
Increased frequency and intensity of visual hallucinations	0(0)	0(0)	1(1)	1(0)
Intermittent cough	1(1)	0(0)	0(0)	1(0)
Lightheadedness	0(0)	0(0)	1(1)	1(0)
Patient experienced throat irritation with coughing and choking sensation after 1st inhalation.	1(1)	0(0)	0(0)	1(0)
Patient hospitalized due to SAE, unable to perform TV4 at the site.	0(0)	1(1)	0(0)	1(0)
SAE - completed suicide	1(1)	0(0)	0(0)	1(0)
Significant worsening of post-dose spirometry results on bl.	0(0)	1(1)	0(0)	1(0)
Tightness in chest	0(0)	1(1)	0(0)	1(0)
All	3(3)	6(5)	3(3)	12(4)
Reason Other				
Did not want to be in the study anymore and wanted to switch	0(0)	0(0)	1(1)	1(0)

to the new medication, Rytary.				
Patient did not meet spirometry criteria	1(1)	0(0)	0(0)	1(0)
Patient was non-compliant to study visits and use of study medication.	0(0)	1(1)	0(0)	1(0)
Subject had a change in Parkinson's medication and no longer met inclusion 9.	0(0)	0(0)	1(1)	1(0)
Unable to come to visits to due work and family commitments	1(1)	0(0)	0(0)	1(0)
All	2(2)	1(1)	2(2)	5(1)

Source: Reviewer

REVIEWER COMMENT:

Twice as many patients withdrew from the study because of an adverse event in the high dose (DL2) group compared to low dose (DL1) group and placebo group (6 versus 3 versus 3.)

Adverse events for DL2 (84mg) leading to discontinuation are shown in Table 37

Table 37 AEs leading to discontinuation in DL2 (Study CVT-301-004)

AEBODSYS	AEDECOD	CVT 301 DL2
Gastrointestinal disorders	Nausea	1
	Vomiting	1
General disorders and administration site conditions	Chest discomfort	1
Infections and infestations	Influenza	1
Investigations	Spirometry abnormal	1
Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	1
	Lumbar spinal stenosis	1
Psychiatric disorders	Initial insomnia	1
	Irritability	1
Respiratory, thoracic and mediastinal disorders	Cough	2
	Dry throat	1

Source: CDTL

REVIEWER COMMENT:

The most common reason adverse events leading to discontinuation in patients in DL2 (84mg) cohort was cough.

ISS

In POOL 1 (CVT-301-004 and CVT-301-003), 270 subjects were treated with CVT-301, of whom 85.9% completed the study. There were 155 subjects in the treated with placebo, of whom 85.8% completed the study (Table 38).

Table 38 Disposition of Subjects in the Integrated Safety Analysis (ISS)

	POOL 1		POOL 2	POOL 3	Observational cohort N=127 n (%)
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)	
Enrolled to study	279	161	603	716	130
Safety population	270	155	583	705	127
Completed the study	232 (85.9)	133 (85.8)	271 (46.5)	355 (50.4)	106 (83.5)
Ongoing at the time of ISS data snapshot			162 (27.8)	162 (23.0)	
Study discontinuations	38 (14.1)	22 (14.2)	150 (25.7)	188 (26.7)	21 (16.5)
Reason for discontinuation					
Adverse event	10 (26.3)	6 (27.3)	42 (28.0)	52 (27.7)	
Lost to follow-up	2 (5.3)	1 (4.5)	5 (3.3)	7 (3.7)	
Protocol deviation			1 (0.7)	1 (0.5)	
Withdrawal by subject	21 (55.3)	13 (59.1)	61 (40.7)	82 (43.6)	18 (85.7)
Lack of efficacy	2 (5.3)		24 (16.0)	26 (13.8)	
Other	3 (7.9)	2 (9.1)	17 (11.3)	20 (10.6)	3 (14.3)

Note: Percentages are based on the safety population; reasons for discontinuation percentages are based on total number of study discontinuations.

POOL 1 includes studies [CVT-301-003](#) and [CVT-301-004](#). POOL 2 includes CVT-301 groups from studies [CVT-301-004E](#) and [CVT-301-005](#). POOL 3 includes CVT-301 groups from all studies ([CVT-301-003](#), [CVT-301-004](#), [CVT-301-004E](#) and [CVT-301-005](#)).

For subjects participating to several studies, the latest discontinuation information was used in POOL 3.

Abbreviation: ISS = Integrated Summary of Safety.

Source: [ISS Table 1.2](#).

Source: Applicant

REVIEWER COMMENT:

The rate of study discontinuations was similar between drug and treatment group. The reasons for discontinuation were similar except for a lack of efficacy which occurred in 5.3% of subjects in the CVT-301 treatment group.

The TEAEs leading to withdrawal, ISS population, are outlined in the table below (Table 39.)

Table 39 Treatment-emergent Adverse Events Leading to Withdrawal from the Study (ISS, Safety Population)

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270	Placebo N=155 n (%)	CVT-301 N=583	CVT-301 N=705
Subjects with adverse event leading to withdrawal	10 (3.7)	6 (3.9)	41 (7.0)	51 (7.2)
Cough	3 (1.1)		9 (1.5)	12 (1.7)
Hallucination		1 (0.6)	3 (0.5)	3 (0.4)
Throat irritation	1 (0.4)		2 (0.3)	3 (0.4)
Bronchitis			2 (0.3)	2 (0.3)
Dyskinesia			2 (0.3)	2 (0.3)
Euphoric mood			2 (0.3)	2 (0.3)
Vision blurred			2 (0.30)	2 (0.3)
Anoxia			1 (0.2)	1 (0.1)
CNS lesion			1 (0.2)	1 (0.1)
Cerebrovascular accident			1 (0.2)	1 (0.1)
Chest discomfort	1 (0.4)			1 (0.1)
Completed suicide	1 (0.4)			1 (0.1)
Dehydration			1 (0.2)	1 (0.1)
Dopamine dysregulation syndrome			1 (0.2)	1 (0.1)
Drug intolerance			1 (0.2)	1 (0.1)
Dry mouth			1 (0.2)	1 (0.1)
Dry throat	1 (0.4)			1 (0.1)

Dyspnea			1 (0.2)	1 (0.1)
Dystonia			1 (0.2)	1 (0.1)
Escherichia urinary tract infection			1 (0.2)	1 (0.1)
Flushing			1 (0.2)	1 (0.1)
Hallucination, visual			1 (0.2)	1 (0.1)
Hip fracture			1 (0.2)	1 (0.1)
Hyperhidrosis			1 (0.2)	1 (0.1)
Hypertension			1 (0.2)	1 (0.1)
Intentional product misuse			1 (0.2)	1 (0.1)
Intervertebral disc protrusion	1 (0.4)			1 (0.1)
Lumbar spinal stenosis	1 (0.4)			1 (0.1)
Metastases to central nervous system			1 (0.2)	1 (0.1)
Nasal congestion			1 (0.2)	1 (0.1)
Nasopharyngitis			1 (0.2)	1 (0.1)
Nausea			1 (0.2)	1 (0.1)
Nephrolithiasis			1 (0.2)	1 (0.1)
Occipital neuralgia			1 (0.2)	1 (0.1)
Orthostatic hypotension			1 (0.2)	1 (0.1)
Painful respiration	1 (0.4)			1 (0.1)
Parkinsonism			1 (0.2)	1 (0.1)
Pulmonary embolism			1 (0.2)	1 (0.1)
Retinal detachment			1 (0.2)	1 (0.1)
Rhabdomyolysis			1 (0.2)	1 (0.1)
Rib fracture			1 (0.2)	1 (0.1)
Salivary hypersecretion			1 (0.2)	1 (0.1)
Spirometry abnormal	1 (0.4)			1 (0.1)

Spondylitis			1 (0.2)	1 (0.1)
Syncope			1 (0.2)	1 (0.1)
Tachycardia			1 (0.2)	1 (0.1)
Upper respiratory tract irritation			1 (0.2)	1 (0.1)
Wheezing			1 (0.2)	1 (0.1)
Bradykinesia		1 (0.6)		
Chest Pain		1 (0.6)		

Dizziness		1 (0.6)		
Osteoporotic fracture		1 (0.6)		
Wrist fracture		1 (0.6)		

Source: CDTL

REVIEWER COMMENT:

In POOL 1, the percent of subjects experiencing TEAEs leading to withdrawal was similar between CVT-301 treatment group and placebo (3.7% and 3.9% respectively) with the cough being the most common cause for withdrawal in the CVT-301 treatment group.

7.3.5 Submission Specific Primary Safety Concerns

As with other dopaminergic drug products, important safety concerns include, impulse control disorder, hallucinations/psychosis, dopamine dysregulation syndrome, orthostatic hypotension and dyskinesia:

A listing of all subjects with adverse events leading to withdrawal from the study is shown in Table 40:

Table 40 Adverse Events Leading to Withdrawal from the Study – ISS

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)
Subjects with an adverse event leading to withdrawal from the study	10 (3.7)	6 (3.9)	47 (8.1)	57 (8.1)
Cough	3 (1.1)		10 (1.7)	13 (1.8)
Hallucination		1 (0.6)	3 (0.5)	3 (0.4)
Throat irritation	1 (0.4)		2 (0.3)	3 (0.4)
Bronchitis			2 (0.3)	2 (0.3)
Dyskinesia			2 (0.3)	2 (0.3)
Dyspnea			2 (0.3)	2 (0.3)
Euphoric mood			2 (0.3)	2 (0.3)
Upper respiratory tract irritation			2 (0.3)	2 (0.3)

Vision blurred			2 (0.3)	2 (0.3)
Anoxia			1 (0.2)	1 (0.1)
Central nervous system lesion			1 (0.2)	1 (0.1)
Cerebrovascular accident			1 (0.2)	1 (0.1)

Chest discomfort	1 (0.4)			1 (0.1)
Completed suicide	1 (0.4)			1 (0.1)
Dehydration			1 (0.2)	1 (0.1)
Dizziness		1 (0.6)	1 (0.2)	1 (0.1)
Dopamine dysregulation syndrome			1 (0.2)	1 (0.1)
Drug intolerance			1 (0.2)	1 (0.1)
Dry mouth			1 (0.2)	1 (0.1)
Dry throat	1 (0.4)			1 (0.1)
Dystonia			1 (0.2)	1 (0.1)
Escherichia urinary tract infection			1 (0.2)	1 (0.1)
Flushing			1 (0.2)	1 (0.1)
Hallucination, visual			1 (0.2)	1 (0.1)
Hip fracture			1 (0.2)	1 (0.1)
Hyperhidrosis			1 (0.2)	1 (0.1)
Hypertension			1 (0.2)	1 (0.1)
Intentional product misuse			1 (0.2)	1 (0.1)
Intervertebral disc protrusion	1 (0.4)			1 (0.1)
Lumbar spinal stenosis	1 (0.4)			1 (0.1)
Metastases to central nervous system			1 (0.2)	1 (0.1)
Metastatic squamous cell carcinoma			1 (0.2)	1 (0.1)
Nasal congestion			1 (0.2)	1 (0.1)
Nasopharyngitis			1 (0.2)	1 (0.1)
Nausea			1 (0.2)	1 (0.1)
Nephrolithiasis			1 (0.2)	1 (0.1)
Occipital neuralgia			1 (0.2)	1 (0.1)
Orthostatic hypotension			1 (0.2)	1 (0.1)
Painful respiration	1 (0.4)			1 (0.1)
Parkinsonism			1 (0.2)	1 (0.1)

Pulmonary embolism			1 (0.2)	1 (0.1)
Retinal detachment			1 (0.2)	1 (0.1)
Rhabdomyolysis			1 (0.2)	1 (0.1)
Rib fracture			1 (0.2)	1 (0.1)
Salivary hypersecretion			1 (0.2)	1 (0.1)
Spirometry abnormal	1 (0.4)			1 (0.1)
Spondylitis			1 (0.2)	1 (0.1)
Syncope			1 (0.2)	1 (0.1)
Tachycardia			1 (0.2)	1 (0.1)
Uterine prolapse			1 (0.2)	1 (0.1)
Wheezing			1 (0.2)	1 (0.1)
Bradykinesia		1 (0.6)		
Chest Pain		1 (0.6)		
Osteoporotic fracture		1 (0.6)		
Wrist fracture		1 (0.6)		

REVIEWER COMMENT:

There were two subjects who withdrew for hallucination; 1 in the placebo cohort of DBPC trial and 1 in the open label study. Four subjects withdrew for dizziness/syncope; 1 in placebo cohort of DBPC trial and 3 in OL trial. Three subjects withdrew for dystonia/dyskinesia, all in OL trials. One subject in the OL trials withdrew for dopamine dysregulation syndrome.

Due to the route of delivery, pulmonary safety issues (shortness of breath, cough, respiratory infections, and decrease in respiratory function) are also of concern.

Pulmonary Safety

Pulmonary function tests (PFTs) were performed at the neurology study sites and at dedicated pulmonary function facilities over the duration of the studies. At the neurology study sites, spirometry was performed by staff trained and qualified by (b) (4) a central spirometry laboratory. At the pulmonary function facilities, spirometry and carbon monoxide diffusing capacity (DLCO) were performed by staff trained and certified by (b) (4) a central pulmonary function testing reviewer.

The following pulmonary safety data were collected:

- Neurology office: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio (%)

- Pulmonary function laboratory: FEV1, FVC, FEV1/FVC ratio (%), DLCO and DLCO adjusted for hemoglobin (Hg)

The FEV1, FEV1/FVC, and DLCO data were presented both as absolute values and as percent of predicted value. Both acute and chronic pulmonary safety was evaluated.

Acute Pulmonary Safety

Acute pulmonary safety evaluations included spirometry assessments before dosing and at 15, 30 and 60 minutes after inhalation of the first dose of study drug (Treatment Visit 1) in the Neurology office in Studies CVT-301-003, CVT-301-004 and CVT-301-004E only.

- Actual values and change from pre-dose to post-dose by time point at Treatment Visit 1 for FEV1, FVC, and FEV1/FVC ratio are summarized.
- Change from pre-dose to post-dose by time point in FEV1/FVC ratio of < 60%, 60 to < 70%, or normal; and in FEV1, FVC and DLCO < 80% of the predicted value or normal are summarized using shift tables.
- Absolute change from pre-dose to post-dose by time point at Treatment Visit 1 in FEV1, FVC, FEV1/FVC ratio and percent of predicted values in FEV1 and FVC were tabulated categorically: $\geq 50\%$, $\geq 40\%$ to $< 50\%$, $\geq 30\%$ to $< 40\%$, $\geq 20\%$ to $< 30\%$, $\geq 10\%$ to $< 20\%$, $> -10\%$ to $< 10\%$, $> -20\%$ to $\leq -10\%$, $> -30\%$ to $\leq -20\%$, $> -40\%$ to $\leq -30\%$, $> -50\%$ to $\leq -40\%$, $\leq -50\%$.

Chronic Pulmonary Safety

Chronic pulmonary safety was assessed by evaluating the change from baseline in spirometry parameters at pulmonary function facilities and neurology sites and DLCO assessments performed at pulmonary function facilities prior to screening and at subsequent treatment visits in all multiple dose studies CVT-301-004, CVT-301-004E, CVT-301-005), except for Study CVT-301-003 as no pulmonary function facilities were used in that study.

- Actual values on arrival to the visit and changes from baseline to each post-baseline visit in arrival values are summarized for FEV1, FVC, FEV1/FVC ratio, DLCO, and DLCO adjusted for Hg.
- Change from baseline to post-baseline in FEV1/FVC ratio of < 60%, 60 to < 70%, or normal; and in FEV1, FVC and DLCO < 80% of the predicted value or normal are summarized using shift tables.

- Absolute change from baseline to post-baseline in FEV1, FVC, FEV1/FVC ratio, DLCO and DCO adjusted for Hg were tabulated categorically by visit: $\geq 50\%$, $\geq 40\%$ to $< 50\%$, $\geq 30\%$ to $< 40\%$, $\geq 20\%$ to $< 30\%$, $\geq 10\%$ to $< 20\%$, $> -10\%$ to $< 10\%$, $> -20\%$ to $\leq -10\%$, $> -30\%$ to $\leq -20\%$, $> -40\%$ to $\leq -30\%$, $> -50\%$ to $\leq -40\%$, $\leq -50\%$.

In addition to descriptive analyses, the changes from baseline were estimated with Mixed Model for Repeated Measures (MMRM) by using the values measured at arrival to the visit. Estimates of mean change and associated 95% confidence intervals by visit are presented. The MMRM model included the changes from baseline in the PFT values from all scheduled post-baseline visits as response variables. The baseline PFT value was included as a covariate and visit and treatment group (when applicable) as fixed factors. If the treatment group was included in the MMRM, also the interaction term between visit and treatment group was included, to estimate the treatment difference at each visit.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was consulted by DNP to review the pulmonary safety results from these studies (Pulmonary Review DARRTS 8/15/2018.) These results are summarized below.

Study CVT-301-004, a randomized, double-blind, placebo-controlled study, patients were randomized to receive CVT-301 60 mg, CVT-301 84 mg or placebo. Serial spirometry was performed at screening, randomization and weeks 4, 8 and 12.

The most common adverse events (AE) in the first 12-weeks of Study 004 were cough, throat irritation, and upper respiratory tract infection.

- Cough occurred in 2 (1.8%) patients on placebo, 17 (15%) patients on CVT-301 60 mg, and 17 (14.9%) on CVT-301 84 mg.
- Throat irritation occurred in 8 (7.1%) patients on CVT- 301 60 mg and 1 (0.9%) patient on CVT-301 84 mg, but not in patients on placebo.
- Upper respiratory infection occurred in 3 (2.7%) patients on placebo, 2 (1.8%) patients on CVT-301 60 mg, and 7 (6.1%) on patients on 84 mg.
- Only cough and throat irritation occurred more in the treatment groups vs. placebo; there was no dose response observed for these common adverse events.

In **Study CVT-301-004E**, an extension study of Study 004, the primary/secondary objectives were to characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry (FEV1, FVC, and FEV1/FVC) and pulmonary adverse events.

All 325 patients were enrolled and randomized to receive active treatment (CVT-301 60 mg (n=161) or CVT-301 84 mg (n=164)). Interpretation of the study results in 004E

were limited by the lack of a control group, and the interim nature of the analysis (study is still ongoing). Noting these major limitations, dose response for pulmonary adverse events and spirometry changes were examined by the pulmonary reviewer;

The most common pulmonary adverse events in Study 004E were cough, throat irritation, oropharyngeal pain, sputum discolored, dyspnea, and dysphonia.

The mean change from baseline in FEV1 at Week 52 for both dose groups was -0.163L and -0.124L, respectively. The magnitude of the change from baseline was inconsistent/variable over time (including at follow-up).

Overall, neither AEs nor spirometry demonstrated a dose response for pulmonary safety signals. Further interpretation of the safety findings in Study 004E is limited due to the lack of a control group.

Study CVT-301- 005 was a randomized, open-label study investigating the pulmonary safety of CVT-301 in Parkinson's disease patients with motor response fluctuations (off phenomena) compared to an observational cohort.

The primary objective was to assess pulmonary function via spirometry (FEV1, FVC, and FEV1/FVC ratio) over a 12-month period. Only CVT-301 naïve patients were enrolled. A total of 408 patients were enrolled; patients were assigned to CVT-301 84 mg (n=278) or to an observational cohort (n=130). The patients in the observational cohort were maintained on their usual medical regimen for Parkinson's disease only and received no inhaled therapies.

Pulmonary serious adverse events (SAEs) occurred only in single patients and did not reveal a pulmonary safety signal. The most frequently reported pulmonary adverse events in the CVT- 301 treatment group and occurring with a greater frequency than in the observational cohort were:

- cough (13% vs. 0.8%),
- sputum discolored (3.3% vs. 0%)
- throat irritation (3.3% vs. 0%).

The majority of the cough adverse events were reported as mild in intensity.

The Applicant submitted results for spirometry, including Forced Expiratory Volume in 1 sec (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratio. Diffusion capacity of carbon monoxide (DLCO) was also examined. All data was reviewed by the pulmonary reviewer; however, the emphasis was placed on FEV1, noting that FVC and DLCO showed similar findings. In addition, the pulmonary review relied upon the results obtained from **pulmonary function facilities** to ensure reliability of the measurements.

- The mean values for FEV1 at Baseline were similar between the treatment arms (2.84 L for the observational cohort and 2.84 L for the CVT-301 treatment group).

- The LS mean differences (95% CI) were
 - o 0.021 (-0.022, 0.063) at TV3/OV3 (Week 12),
 - o 0.033 (-0.010, 0.077) at TV4/OV4 (Week 24),
 - o 0.022 (-0.027, 0.071) at TV5/OV5 (Week 36),
 - o 0.002 (-0.046, 0.050) at TV6/OV6 (Week 52);

None of these differences were clinically or statistically significant. Findings for FVC and DLCO revealed similar results.

DPARP consultants concluded that, while individual patients appeared to have reductions in FEV1>12% which would meet the criteria of bronchial hyperresponsiveness, the concern for this as a safety signal is weakened by the lack of symptoms, improvement without rescue medications, and the fact that 4 of these patients had similar FEV1 reductions in response to placebo. Further, the mean changes from baseline in both absolute and percent predicted FEV1 did not meet ATS criteria for bronchial hyperresponsiveness. Overall, there are no pulmonary safety signals that preclude approval of Inbrija.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CVT-301-004

Common adverse events for the pivotal efficacy study, CVT-301-004 were analyzed using MAED tool and are presented in the table below (Table 41.)

Table 41 Study CVT 301 004 - Adverse Reactions $\geq$ 2% DL1 or DL2 and Higher than Placebo

AEBODSYS	AEDECOD	CVT 301 DL1 N=113 %	CVT 301 DL 2 N=114 %	Placebo N=112 %
Respiratory, thoracic and mediastinal disorders	Cough	15	15	2
Infections and infestations	Upper respiratory tract infection	2	6	3

Gastrointestinal disorders	Nausea	0	5	3
Respiratory, thoracic and mediastinal disorders	Sputum discolored	0	5	0
Nervous system disorders	Dyskinesia	4	4	0
Gastrointestinal disorders	Vomiting	0	3	0
Infections and infestations	Nasopharyngitis	2	3	2
Injury, poisoning and procedural complications	Fall	4	3	2
General disorders and administration site conditions	Chest discomfort	0	2	0
Injury, poisoning and procedural complications	Laceration	2	2	0
Injury, poisoning and procedural complications	Skin abrasion	0	2	0
Investigations	Blood bilirubin increased	1	2	0
Investigations	Red blood cell count decreased	1	2	0
Musculoskeletal and connective tissue disorders	Pain in extremity	2	2	1
Nervous system disorders	Headache	4	2	0
Psychiatric disorders	Hallucination	2	2	2
Psychiatric disorders	Insomnia	1	2	1
Respiratory, thoracic and mediastinal disorders	Nasal discharge discoloration	2	2	0
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0	2	0
Infections and infestations	Influenza	4	1	0
Infections and infestations	Urinary tract infection	3	1	0
Musculoskeletal and connective tissue disorders	Back pain	4	1	0
Respiratory, thoracic and mediastinal disorders	Throat irritation	7	1	0
Vascular disorders	Hypertension	2	1	1
Gastrointestinal disorders	Flatulence	2	0	0
General disorders and administration site conditions	Chest pain	2	0	0
General disorders and administration site	Pyrexia	3	0	0

conditions				
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	2	0	1
Nervous system disorders	Paraesthesia	2	0	0

Source: Reviewer

REVIEWER COMMENT:

The most common adverse event in both active treatment groups was cough (15%) versus placebo (2%.) Dyskinesias were also more common in active treatment groups (4%) versus placebo (0.0%). Hallucinations were similar across all treatment groups (2%.)

ISS

Common adverse events for the double blind placebo controlled studies, POOL 1 and long terms studies (POOL 2) are presented in the table below (Table 42).

Table 42 Treatment-emergent Adverse Events Reported for ≥2% of Subjects by Pool (Safety Population)

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)
Cough	37 (13.7)	3 (1.9)	80 (13.7)	110 (15.6)
Fall	8 (3.0)	3 (1.9)	56 (9.6)	61 (8.7)
Upper respiratory tract infection	9 (3.3)	3 (1.9)	32 (5.5)	41 (5.8)
Dyskinesia	10 (3.7)	1 (0.6)	32 (5.5)	40 (5.7)
Nasopharyngitis	5 (1.9)	2 (1.3)	29 (5.0)	33 (4.7)
Throat irritation	9 (3.3)	1 (0.6)	20 (3.4)	29 (4.1)
Back pain	6 (2.2)		22 (3.8)	26 (3.7)
Nausea	9 (3.3)	3 (1.9)	12 (2.1)	21 (3.0)
Sputum discolored	8 (3.0)		13 (2.2)	20 (2.8)
Urinary tract infection	5 (1.9)	1 (0.6)	14 (2.4)	19 (2.7)
Dizziness	6 (2.2)	7 (4.5)	14 (2.4)	19 (2.7)
Arthralgia			17 (2.9)	17 (2.4)
Headache	8 (3.0)	2 (1.3)	8 (1.4)	16 (2.3)

Pain in extremity	4 (1.5)	1 (0.6)	12 (2.1)	15 (2.1)
Hallucination	4 (1.5)	2 (1.3)	10 (1.7)	14 (2.0)
Oropharyngeal Pain	2 (0.7)	1 (0.6)	12 (2.1)	14 (2.0)
Influenza	6 (2.2)		8 (1.4)	14 (2.0)
Constipation	2 (0.7)	1 (0.6)	12 (2.1)	14 (2.0)
Hypertension	3 (1.1)	1 (0.6)	11 (1.9)	14 (2.0)
Laceration	5 (1.9)		9 (1.5)	14 (2.0)

Only patients treated with CVT 301-excludes untreated Observational Cohort

Source: Applicant

REVIEWER COMMENT:

In the ISS cough was the most common adverse event in both double blind placebo controlled (POOL 1) on CVT-301 and long term studies (POOL 2).

7.4.2 Laboratory Findings

Study CVT-301-004

In study CVT-301-004, there were no notable differences in shifts from baseline to TV4 or Follow-up Visit in hematology or chemistry values.

ISS

There were no significant abnormalities in hematology or chemistry values.

Patients with liver function test results that shifted from normal or low to high are presented in the table below (Table 43).

Table 43 ISS Patients with Liver Chemistry Shift from Normal or Low to High

USUBJID	ACTARM	PARAM	BASE	AVALC	SHIFT1	CRIT1	CRIT3	ANRLO	ANRHI
CVT-301-005-(b) (6)	CVT-301 50 mg	Aspartate Aminotransferase (U/L)	25	107	NORMAL to HIGH	AST > 3 x ULN	AST > 3 x ULN	14	34
CVT-301-005-(b) (6)	CVT-301 50 mg	Bilirubin (umol/L)	15.6	32.8	NORMAL to HIGH	Total bilirubin > 1.5 * ULN	Total bilirubin > 1.5 * ULN	5.1	20.5
CVT-301-005-(b) (6)	CVT-301 50 mg	Bilirubin (umol/L)	16.7	41.3	NORMAL to HIGH	Total bilirubin > 1.5 *	Total bilirubin > 1.5 *	5.1	20.5

CVT-301-004-(b) (6)	CVT 301 DL1	Bilirubin (umol/L)	15.8	38.8	NORMAL to HIGH	ULN Total bilirubin > 1.5 * ULN	ULN Total bilirubin > 1.5 * ULN	5.1	20.5
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Source: CDTL

REVIEWER COMMENT:

There were no cases that met the criteria for Hy's Law.

7.4.3 Vital Signs

No significant difference between treatment groups for vital signs. Vital signs for orthostatic changes were analyzed for treatment groups during double blind placebo controlled phase using JMP Clinical (ISS Pool 1 120 day safety update) (Figures 14-16)

Figure 14 Orthostatic Change - Diastolic Blood Pressure (mmHg) Results

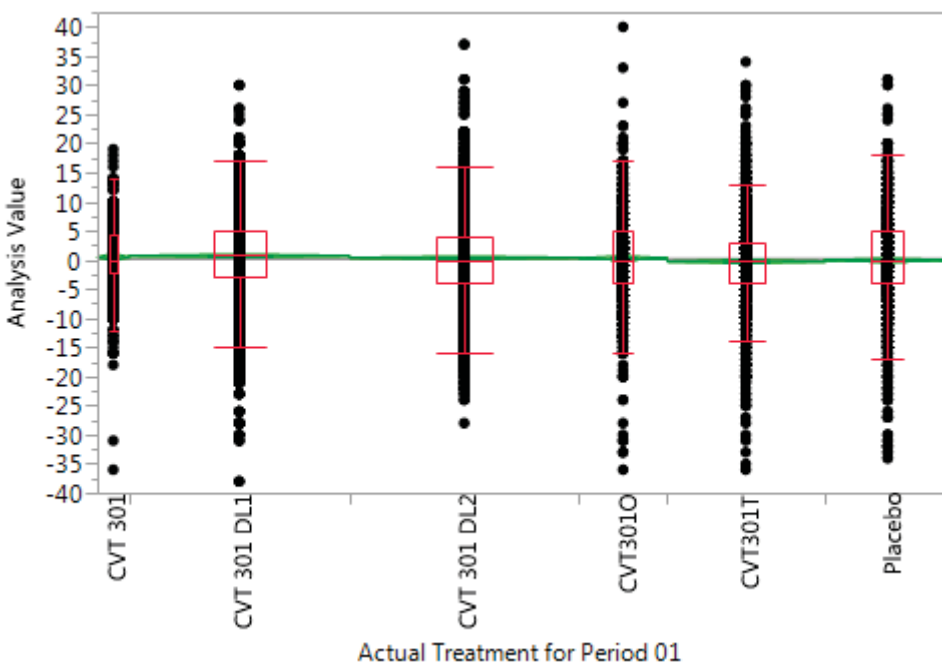
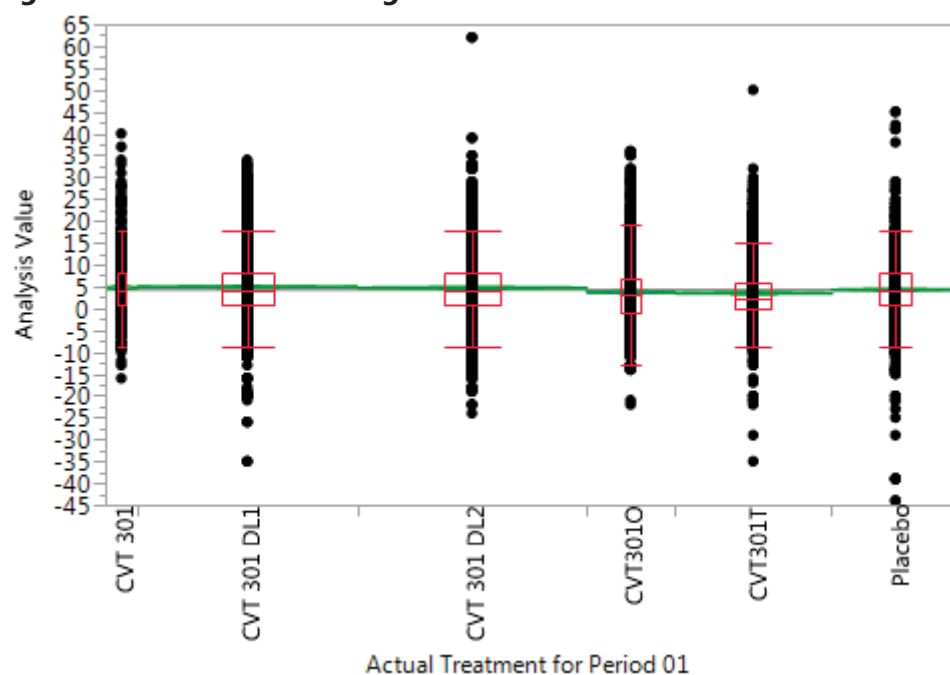
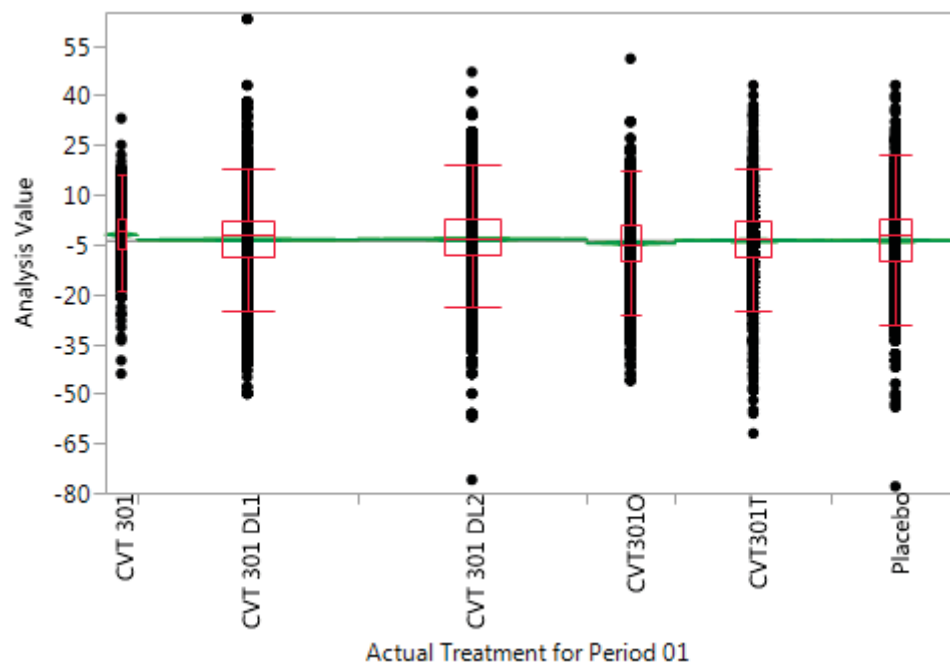


Figure 15 Orthostatic Change - Heart Rate Results**Figure 16 Orthostatic Change - Systolic Blood Pressure (mmHg) Results**

Source: CDTL

REVIEWER COMMENT:

Orthostatic changes for systolic and diastolic blood pressure and heart rate did not show any meaningful differences between treatment groups.

7.4.4 Electrocardiograms (ECGs)

ECG results were reviewed for the safety database. Overall there was one subject in Pool 1 who had an increase in QTcF>60ms compared to baseline (349 msec to 417 msec) at any time point (Table 44.)

Table 44 QTcF Change from Baseline

6 Other safety: ECG

6.9 QTcF, outlier analysis

Table 6.9.1 QTcF, change from baseline prior to dose

Safety population

Analysis Visit	Category (%p)	Pool 1		Pool 2		Pool 3	
		CVT-301 n (%)	Placebo n (%)	CVT-301 n (%)	CVT-301 n (%)	CVT-301 n (%)	CVT-301 Observational Cohort n (%)
MONTH 1-3	Normal Change	251 (98.0)	146 (100.0)	521 (98.9)	640 (98.3)	113 (98.3)	
	Increment > 30 ms	5 (2.0)		6 (1.1)	11 (1.7)	2 (1.7)	
	Increment 30-60 ms	4 (1.6)		6 (1.1)	10 (1.5)	2 (1.7)	
	Increment > 60 ms	1 (0.4)			1 (0.2)		
MONTH 6	Normal Change			455 (98.1)	463 (98.1)	108 (97.3)	
	Increment > 30 ms			9 (1.9)	9 (1.9)	3 (2.7)	
	Increment 30-60 ms			9 (1.9)	9 (1.9)	3 (2.7)	
	Increment > 60 ms						
MONTH 9	Normal Change			116 (99.1)	163 (98.2)		
	Increment > 30 ms			1 (0.9)	3 (1.8)		
	Increment 30-60 ms			1 (0.9)	3 (1.8)		
	Increment > 60 ms						

6 Other safety: ECG

6.9 QTcF, outlier analysis

Table 6.9.1 QTcF, change from baseline prior to dose

Safety population

Analysis Visit	Category (%p)	Pool 1		Pool 2		Pool 3	
		CVT-301 n (%)	Placebo n (%)	CVT-301 n (%)	CVT-301 n (%)	CVT-301 n (%)	CVT-301 Observational Cohort n (%)
MONTH 12	Normal Change			272 (96.5)	298 (96.4)	104 (97.2)	
	Increment > 30 ms			10 (3.5)	11 (3.6)	3 (2.8)	
	Increment 30-60 ms			10 (3.5)	11 (3.6)	3 (2.8)	
	Increment > 60 ms						
MONTH 15	Normal Change				50 (98.0)		
	Increment > 30 ms				1 (2.0)		
	Increment 30-60 ms				1 (2.0)		
	Increment > 60 ms						
Overall	Normal Change	250 (96.5)	145 (97.3)	536 (95.7)	644 (95.1)	116 (95.9)	
	Increment > 30 ms	9 (3.5)	4 (2.7)	24 (4.3)	33 (4.9)	5 (4.1)	
	Increment 30-60 ms	8 (3.1)	4 (2.7)	24 (4.3)	32 (4.7)	5 (4.1)	
	Increment > 60 ms	1 (0.4)			1 (0.1)		

Source dataset: adam.adeg

NOTE: POOL 1 includes studies CVT-301-003 and CVT-301-004. POOL 2 includes CVT-301 groups from studies CVT-301-004E and CVT-301-005. POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005).

NOTE: The overall row summarizes abnormal changes occurring at least once during the study/ studies including also values excluded from the by visit data (i.e. unscheduled measurements). In this row 'normal' category includes subjects with no abnormal changes during the study/ studies.

Program: t6-9qtcf-outlier.sas [06SEP2017/18:07]

Source: Applicant

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant used the following Preferred Terms to assess for Adverse Events potentially related to drug abuse (Table 45.)

Table 45 Treatment-emergent Adverse Event Preferred Terms of Events Potentially Related to Drug Abuse

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 synaesthetic
Hallucination tactile	Hallucination visual	Hedonistic homeostatic dysregulation	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			

Source: Applicant

An analysis of TEAEs potentially related to drug abuse using the above terms for the safety population is presented in the table below (Table 46).

Table 46 Treatment-emergent Adverse Events Potentially Related to Drug Abuse (Safety Population)

	POOL 1		POOL 2	POOL 3	Observational cohort N=127 n (%)
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)	
Any event	14 (5.2)	9 (5.8)	29 (5.0)	41 (5.8)	4 (3.1)
Dizziness	6 (2.2)	7 (4.5)	13 (2.2)	18 (2.6)	1 (0.8)
Hallucination	4 (1.5)	2 (1.3)	10 (1.7)	14 (2.0)	1 (0.8)
Hallucination, visual			3 (0.5)	3 (0.4)	1 (0.8)
Somnolence	2 (0.7)	2 (1.3)		2 (0.3)	1 (0.8)

Euphoric mood			2 (0.3)	2 (0.3)	
Feeling abnormal			1 (0.2)	1 (0.1)	
Intentional product misuse			1 (0.2)	1 (0.1)	
Cognitive disorder			1 (0.2)	1 (0.1)	
Disturbance in attention			1 (0.2)	1 (0.1)	
Dizziness postural			1 (0.2)	1 (0.1)	
Memory impairment					1 (0.8)
Agitation	1 (0.4)			1 (0.1)	
Dopamine dysregulation syndrome			1 (0.2)	1 (0.1)	
Irritability	1 (0.4)			1 (0.1)	
Paranoia	1 (0.4)			1 (0.1)	
Psychotic disorder			1 (0.2)	1 (0.1)	
Confusional state		1 (0.6)			
Orthostatic hypotension ^a			1 (0.2)	1 (0.1)	

Note: POOL 1 includes studies CVT-301-003 and CVT-301-004. POOL 2 includes CVT-301 groups from studies CVT-301-004E and CVT-301-005. POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005).

^a Verbatim term was “dizziness (orthostatic hypotension).”

Source: ISS Table 3.16.1.1.

Source: Applicant

REVIEWER COMMENT:

The rate and type of TEAEs potentially related to drug abuse in POOL 1, was similar between CVT-301 treatment group and placebo (5.2% versus 5.8% respectively.)

The Division consulted the Controlled Substance Staff (CSS) to review the application for evidence of withdrawal, abuse or misuse of CVT-301. In a memo to the Division, Dr. Chiapperino, Division Director, noted that although there were some gaps in the applicant's data collection, there was no convincing evidence of a withdrawal syndrome after discontinuation of CVT-301 and does not recommend any additional clinical studies of dependence and/or withdrawal. In addition, there was no clear evidence of abuse of CVT-301, in the application. Although there were rare cases associated with Dopamine Dysregulation Syndrome, Dr. Chiapperino did not recommend any additional language other than the class language in Warnings and Precautions that is already included in all dopaminergic drug labels (DARRTS 12/18/2018.)

SUMMARY OF SAFETY:

One death occurred during the double blind placebo controlled trials and one death in the open label pulmonary safety study. One subject on DL1(60mg), in the pivotal study, CVT-301-004, committed suicide. The second subject on DL2 in the open label pulmonary safety study, drowned (hypoxic/anoxic encephalopathy.) Of note, the subject in the pulmonary safety study had a change in pulmonary function tests, 10 days prior to the incident. There was a -23.2% change in FEV1, -18.8% change in FVC, and FEV1/FVC ratio change of -5.7%. There was no significant history of pulmonary disease except for remote history of smoking.

The frequency of hallucinations, dyskinesias, impulse control disorder and orthostatic hypotension was low across all studies. The most common adverse event for patients taking CVT-301 was cough. This is most likely due to the route of administration, inhalation. Pulmonary function testing was included as part of the safety monitoring plan. The results of pulmonary function testing in placebo controlled and long term studies were reviewed by DPARP. The DPARP review team concluded that there were no safety signals in pulmonary function testing that would preclude the approval of Inbrija.

There was no clinically significant laboratory, vital sign, or ECG findings during the studies.

Pediatrics

The applicant had an agreed initial Pediatric Study Plan and the application included a Pediatric Plan with a request for a full waiver from pediatric studies required under the Pediatric Research Equity Act (PREA.) The applicant's rationale that PD occurs primarily in the adult population and disease is extremely rare in the pediatric population would be impossible or highly impractical to conduct was found to be supportive of the request for a full waiver. The Pediatric Research Committee (PeRC) granted the applicant's full request.

9 Labeling Recommendations

The proposed product label including the instructions for use and patient package insert comprise the documents included in the proposed labeling. Labeling discussion with the applicant is ongoing.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSANNE R GOLDSTEIN
12/21/2018

GERALD D PODSKALNY
12/21/2018

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: August 15, 2018
To: Stacy Metz, Senior Regulatory Project Manager, DNP
From: Mary O'Donnell, Medical Officer DPARP
Through: Banu Karimi-Shah, Medical Team Leader, DPARP
Subject: Pulmonary Safety and Labeling of Inhaled Dry Powder Levodopa

General Information

NDA: NDA 209184
Sponsor: Acorda Therapeutics
Drug Product: CVT-301 (inhaled dry powder levodopa)
Request From: Billy Dunn, MD, Acting Division Director, Division of
Neurology Products
Date of Request: April 18, 2018
Date Received: April 18, 2018
Materials Reviewed: NDA 209184, CVT-301-008, CVT-301-004E and CVT-301-
005 protocols, eCTD 0008

I. Executive Summary

This is a Medical Officer response to the request for consultation from the Division of Neurology Products (DNP) to provide comments on the pulmonary safety results for CVT-301 (levodopa inhalation powder), which is being reviewed in its second NDA review cycle, after having received a Complete Response on March 16, 2009. The CVT-301 delivery system is a capsule-based, breath-actuated inhaler. Inhalation is a new route of administration for levodopa. Acorda Therapeutics submitted this NDA for CVT-301 as a 505(b)(2) NDA, referencing carbidopa/levodopa (CD/LD) tablets 25mg/100mg (Sinemet®, NDA 01755, approved May1975). The proposed indication is treatment of episodic motor fluctuations (or OFF episodes) in patients with Parkinson's disease (PD) to be used as an as-needed (PRN) adjunct to a carbidopa/levodopa regimen. The proposed dosing regimen is up to five inhalations per day (2 capsules/inhalation, 84 mg/inhalation, 420 mg maximum total daily dose), as needed. Each capsule contains 42 mg of levodopa (active ingredient), 1,2 dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), and sodium chloride.

While the safety of orally administered levodopa is well-known, the local pulmonary safety was unknown given the new inhalation route of administration. DPARP has provided consultation on multiple occasions as to the pulmonary safety data required to support registration of inhaled dry powder levodopa. The Applicant has complied with DPARP recommendations throughout development; we are now consulted by DNP to review the pulmonary safety data, including the pulmonary adverse events and pulmonary function tests submitted to support the NDA in Studies CVT-301-004E (Study 004E), CVT-301-005 (Study 005), and CVT-301-008 (Study 008).

The safety data in each of the clinical study reports was reviewed and a summary of the data is provided below. The Executive Summary is followed by DPARP's labeling recommendations in Section II. A more detailed review of each clinical study, with respect to the pulmonary safety is provided in Section III. A summary of the regulatory history as it pertains to previous DPARP consults is provided Section IV for reference.

Study 004E was a 12-month, dose-level blinded, multicenter study of 2 inhaled dose levels (DL1 60 mg or DL2 84 mg) of CVT-301 for the treatment of up to 5 OFF periods per day in Parkinson's Disease patients with motor response fluctuations (off phenomena). This was an extension of CVT-301-004 (Study 004), a 12-week efficacy/safety study of inhaled CVT-301 compared with placebo in Parkinson's Disease (PD) patients experiencing motor response fluctuations. In Study 004, a randomized, double-blind, placebo-controlled study, patients were randomized to receive CVT-301 60 mg, CVT-301 84 mg or placebo. Serial spirometry was performed at screening, randomization and weeks 4, 8 and 12. The most common adverse events (AE) in the first 12-weeks of Study 004 were cough, throat irritation, and upper respiratory tract infection. Cough occurred in 2 (1.8%) patients on placebo, 17 (15%) patients on CVT-301 60 mg, and 17 (14.9%) on CVT-301 84 mg. Throat irritation occurred in 8 (7.1%) patients on CVT-301 60 mg and 1 (0.9%) patient on CVT-301 84 mg, but not in patients on placebo. Upper respiratory infection occurred in 3 (2.7%) patients on placebo, 2 (1.8%) patients on CVT-301 60 mg, and 7 (6.1%) on patients on 84 mg. Only cough and throat irritation occurred more in the treatment groups vs. placebo; there was no dose response observed for these common adverse events.

In Study 004E, an extension study of Study 004, the primary/secondary objectives were to characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry (FEV1, FVC, and FEV1/FVC) and pulmonary adverse events. All 325 patients were enrolled and randomized to receive active treatment (CVT-301 60 mg (n=161) or CVT-301 84 mg (n=164)). Interpretation of the study results in 004E were limited by the lack of a control group, and the interim nature of the analysis (study is still ongoing). Noting these major limitations, dose response for pulmonary adverse events and spirometry changes were examined by this reviewer; however, the results of Study 005 were relied upon primarily to draw conclusions regarding pulmonary safety. The most common pulmonary adverse events in Study 004E were cough, throat irritation, oropharyngeal pain, sputum discolored, dyspnea, and dysphonia. The mean change from baseline in FEV1 at Week 52 for both dose groups was -0.163L and -0.124L, respectively. The magnitude of the change from baseline was inconsistent/variable over time (including at follow-up). Overall, neither AEs nor spirometry demonstrated a dose response for pulmonary safety signals. Further interpretation of the safety findings in Study 004E is limited due to the lack of a control group.

Study 005 was a randomized, open-label study investigating the pulmonary safety of CVT-301 in Parkinson's disease patients with motor response fluctuations (off phenomena) compared to an observational cohort. The primary objective was to assess pulmonary function via spirometry (FEV1, FVC, and FEV1/FVC ratio) over a 12-month period. Only CVT-301 naïve patients were enrolled. A total of 408 patients were enrolled; patients were assigned to CVT-301 84 mg (n=278) or to an observational cohort (n=130). The patients in the observational cohort were

maintained on their usual medical regimen for Parkinson's disease only and received no inhaled therapies.

Pulmonary serious adverse events (SAEs) occurred only in single patients, and did not reveal a pulmonary safety signal. The most frequently reported pulmonary adverse events in the CVT-301 treatment group and occurring with a greater frequency than in the observational cohort were: cough (13% vs. 0.8%), sputum discolored (3.3% vs. 0%), and throat irritation (3.3% vs. 0%). The majority of the cough adverse events were reported as mild in intensity.

The Applicant submitted results for spirometry, including Forced Expiratory Volume in 1 sec (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratio. Diffusion capacity of carbon monoxide (DLco) was also examined. All data was reviewed, however, the emphasis was placed on FEV1, noting that FVC and DLco showed similar findings. In addition, this review relied upon the results obtained from pulmonary function facilities to ensure reliability of the measurements.

The mean values for FEV1 at Baseline were similar between the treatment arms (2.84 L for the observational cohort and 2.84 L for the CVT-301 treatment group). The LS mean differences (95% CI) were 0.021 (-0.022, 0.063) at TV3/OV3 (Week 12), 0.033 (-0.010, 0.077) at TV4/OV4 (Week 24), 0.022 (-0.027, 0.071) at TV5/OV5 (Week 36), and 0.002 (-0.046, 0.050) at TV6/OV6 (Week 52); none of these differences were clinically or statistically significant. Findings for FVC and DLCO revealed similar results.

CVT-301-008 was a phase 2b, multiple dose, randomized, double-blind, placebo-controlled, 2-period crossover study investigating the safety and PK of inhaled CVT-301 84 mg compared to placebo in 26 asthmatic patients (without Parkinson's disease).

Cough was the most frequent respiratory AE occurring in 15 (60%) of CVT-301 treated patients, was mild (12%) to moderate (48%) in severity, occurred immediately after the dose of CVT-301 and was self-limited. There were no reports of cough or respiratory symptoms following administration of placebo.

Ten of 25 subjects who received CVT-301 had reductions in FEV1 > 15% ranging from 15% - 59% from 15 minutes to 12 hours post dose. Four of the 10 patients who had this reduction also had >15% reduction in FEV1 (15% to 47%) following administration of placebo. These decline were reversible, asymptomatic, and did not require rescue medications to be administered. While individual patients appeared to have reductions in FEV1 > 12% which would meet the criteria of bronchial hyperresponsiveness, the concern for this as a safety signal is weakened by the lack of symptoms, improvement without rescue medications, and the fact that 4 of these patients had similar FEV1 reductions in response to placebo. Further, the mean changes from baseline in both absolute and percent predicted FEV1 did not meet ATS criteria for bronchial hyperresponsiveness.

Overall, there are no pulmonary safety signals that preclude approval of Inbrija.

II. DPARP Labeling Recommendations

We have provided a summary of our recommendations on the package insert relevant to our review of the pulmonary safety, by section. If during DNP's labeling review, you would like for us to edit the label directly, or have further questions, please send us a link to the label and we can provide our comments there as well.

- **Section 5: Warnings and Precautions**

Section 5.1 is proposed to describe bronchospasm in patients with lung disease. We do not have issue with the wording proposed by the sponsor. Based on our evaluation of the FEV1 reductions in this program, the safety signal is not very strong. While we agree that it could remain in Section 5 as a warning, we would recommend reordering based on your evaluation of the other warnings/precautions, as we don't feel that the evidence of bronchospasm in this program warrants being listed as the first W&P.

- **Section 6.1 Adverse Reactions/Clinical Trial Experience**

The discussion of Adverse Reactions in Study 2 adequately covers the pulmonary function findings. In the absence of any difference between treatment groups, DPARP does not believe that Figures 1 and 2 are necessary, and could be deleted.

- **Section 12.3 Pharmacokinetics**

This section describes the differences in exposure between smokers and non-smokers. We defer to the clinical pharmacology reviewers as to the labeling language for this section.

III. Review of the Individual Studies

1. CVT-301- 004E

Study Design

This was a 12-month, dose-level blinded, multicenter study of 2 inhaled dose levels 60mg (DL1) or 84 mg (DL2) of CVT-301 for the treatment of up to 5 OFF periods per day in Parkinson's Disease patients with motor response fluctuations (off phenomena). The primary objective was to characterize the effects of CVT-301 on pulmonary safety, as assessed by absolute change from baseline in FEV1, FVC, and FEV1/FVC over a 12 month period. Secondary safety objectives relevant to pulmonary safety also included characterization of DLco in CVT-301 treated patients. Adverse events (including pulmonary AEs) were also collected.

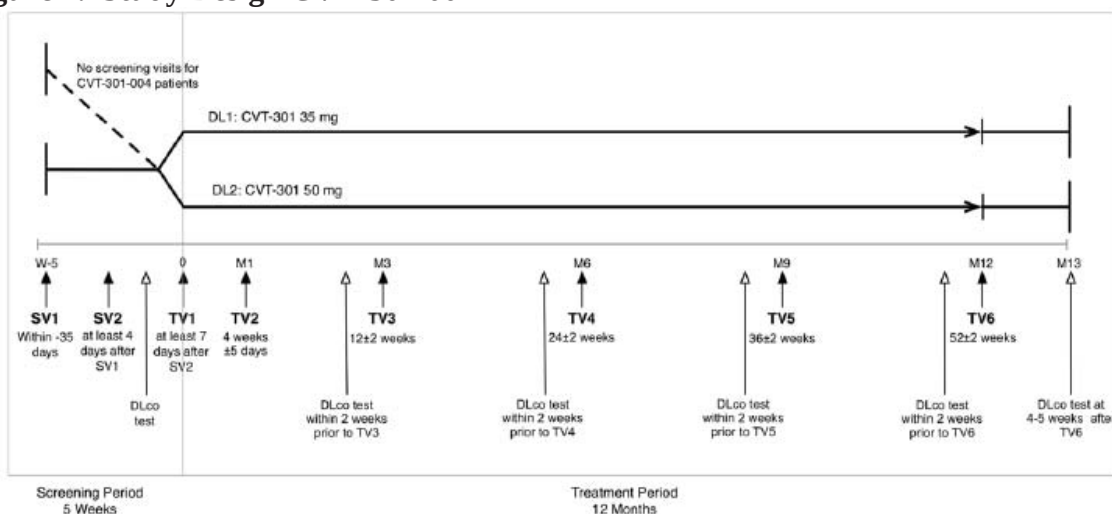
Study 004E was an extension study of the 12-week, double-blinded, safety and efficacy study, Study 004 and enrolled patients from Studies 004, 003, 009, and 005. CVT-301 naïve patients could also be enrolled. Patients who received CVT-301 in Study 004 could remain on their same

blinded dose level: patients who received 60 mg or 84 mg in Study 004 received the same corresponding dose level in Study 004E. Patients who received placebo in Study 004, and all former Study 003 and Study 009 patients, as well as any CVT-301 naïve patients (including patients from the observational arm of Study 005), were randomized in 1:1 ratio to either dose in Study 004E study. Randomization was stratified by screening spirometry (forced expiratory volume in 1 second [FEV1] <60% of predicted or FEV1/FVC ratio <70% versus FEV1 ≥60% of predicted and FEV1/FVC ratio ≥70%). For the patients who received placebo in Study 004, the differentiation of Study 004 was used for randomization for spirometry categories.

The study included a Screening Period of up to 35 days (for CVT-301 naïve patients and patients from Studies 003 and 009) and a Treatment Period of approximately 13 months. The screening visits were not required for Study 004 patients. Study 004 patients had a 1- to 14-day period between the last dose of study drug in Study 004 study and the first dose of study drug in this study. Planned visits occurred at 0 and approximately 1, 3, 6, 9, and 14 months.

A screening period (visits 1 and 2) within 35 days (for CVT-301 naïve patients and patients from the CVT-301-003 and CVT-301-009 study) prior to the treatment period was not required for CVT-301-004 patients. For CVT-301 naïve patients and patients from Study CVT-301-009, spirometry was assessed at the neurology sites for Screening and Treatment Visit 1 (TV1). The baseline DL_{co} was performed at dedicated pulmonary function facilities before TV1 and the pulmonary function facilities were exclusively responsible for the conduct of spirometry and DL_{co} after TV1. Study 004 patients had a 1- to 14-day period between the last dose of study drug in Study 004 study and the first dose of study drug in this study. The Treatment Period was approximately 13 months (56±2 weeks) and planned visits occurred at 0, approximately 1, 3, 6, 9, and 14 months.

Figure 1. Study Design CVT-301-004E



Abbreviations: DL1 = dose level 1; DL2 = dose level 2; DL_{co} = carbon monoxide diffusion capacity; M = month; SV = Screening Visit; TV = Treatment Visit; W = weeks.

Note: CVT-301 35 mg and CVT-301 50 mg refer to the fine particle dose.

Spirometry was performed on the same day as the DL_{co} test.

Source: Study CVT-301-004E CSR Figure 1 pg 27

Pertinent Pulmonary Inclusion Criteria (CVT-301-004E)

- Male or female aged 30-86 years of age
- If the patient is a current or former smoker, has no history of, nor has ever been treated for any smoking-related pulmonary condition (e.g., chronic bronchitis, emphysema, chronic obstructive pulmonary disease [COPD]) or asthma, and has no evidence of obstructive lung disease by spirometry assessment. Patient must agree to abstain from smoking on the day of each in-clinic visit from waking through completion of all assessments for that visit day.
- Has a screening FEV1 $\geq$ 50% of predicted for race, age, sex, and height, and FEV1/FVC ratio $>$ 60%, in the ON state at Screening.

Pertinent Pulmonary Exclusion Criteria

- Patients who had been withdrawn from CVT-301-004, CVT-301-003, CVT-301-009 or CVT-301-005
- Has a history of COPD, asthma, or other chronic respiratory diseases within the last 5 years
- Has any contraindication to performing routine spirometry
- Symptomatic orthostatic hypotension

Smoking Restrictions (listed under Prohibited Medications in the Study Report):

Smokers had to agree to and had to be able to abstain from smoking on the day of each in-clinic visit while in-clinic through completion of all assessments for that visit day (including Screening Visits and in-clinic treatment visits).

Spirometry

Pulmonary function was measured by spirometry using the guideline specified by the Third National Health and Nutrition Examination Survey III (Hankinson 1999). Spirometry assessments were done within 2 weeks prior to the 3-, 6-, 9-, and 12 month study visits and 4 to 5 weeks following completion of Treatment Visit 6. The patient's motor state at the time of each spirometry assessment was recorded. Pulmonary function testing was performed at neurology study sites and at dedicated pulmonary function facilities. Spirometry equipment was provided to each neurology study site to perform the assessments. Spirometry was performed by staff at neurology study sites that were trained and qualified by a central spirometry laboratory and spirometry performed at the pulmonary function facilities were performed by staff that were certified by a central pulmonary function testing reviewer. Quality over-read of all spirometry efforts was done based on acceptability and repeatability metrics in accordance with ATS criteria recommendations (Miller 2005). Spirometry at both neurology study sites and pulmonary function facilities was performed with the goal of meeting ATS acceptability and repeatability criteria. Whether or not the efforts met ATS criteria, FEV1, FVC, and FEV1/FVC ratio were recorded from the single best test (based on effort with highest summed FEV1 and FVC). After Screening, if no acceptable efforts were obtained, the values from the effort with the highest summed FEV1 and FVC were reported.

Screening

Spirometry was performed at the neurology study sites at Screening. At SV1, spirometry assessments were done both while the patient was in the ON and OFF states. Pulmonary safety monitoring and event adjudication was established to identify pulmonary function data indicating that a patient may have pulmonary abnormalities that would not be suitable for inclusion in the study. A pulmonologist reviewed the spirometry tracings/morphology of any patient with an FEV1 that was $\geq 50\%$ to $< 60\%$ of predicted or an FEV1/FVC ratio that was $> 60\%$ to $< 70\%$ at Screening completed spirometry before and after the administration of a bronchodilator in a pulmonary function facility. The results of the bronchodilator challenge were reviewed by a pulmonologist before potential randomization.

Acute Pulmonary Safety

Pulmonary safety monitoring and event adjudication was established to identify pulmonary function data indicating that a patient may have pulmonary abnormalities that would not be suitable for inclusion in the study. In conjunction with the Drug Safety Monitoring Board (DSMB) pulmonary safety monitoring and event adjudication processes were designed to identify trends in pulmonary safety at the patient and study level.

At TV1, after implementation of protocol Version 4.0, spirometry evaluations were performed at the neurology study site immediately before inhalation of CVT-301, and at multiple post-dose time points (15, 30, and 60 minutes) for evaluation of acute pulmonary safety. If within the first 60 minutes after inhalation, the patient's spirometry assessment showed either of the following, the site followed the Spirometry Alert and Review Process: a decrease in FEV1 $\geq 20\%$ AND a decrease in FEV1 by 200 mL compared with pre-dose results, and/or a reduction in the FEV1/FVC ratio to $< 60\%$. If either criteria were met, the patient was not sent home with study drug and the following procedures were followed: (1) any emergent medical conditions were managed as needed; (2a) a Spirometry Alert and Review Worksheet was completed, including documentation of medical assessments and the presence/absence of pulmonary and any other signs or symptoms were recorded, and the worksheet was transmitted to prespecified personnel; (2b) the spirometry assessments were immediately transmitted to the Spirometry Core Laboratory; and (3) all other TV1 safety assessments were completed. The site ensured that the patient was clinically stable before leaving the site. The medical monitor and Acorda determined whether or not the patient could continue study participation. If the patient was cleared to continue study participation, TV1 was repeated in its entirety.

Reviewer's comment: There were 6 subjects who met this criteria at TV1, 4 in the CVT-301 DL1 cohort and 2 in the CVT-301 DL2 cohort. Two subjects, 1 from each cohort discontinued as a result of pulmonary adjudication.

Chronic Pulmonary Safety

Until protocol amendment Version 4.0, spirometry was assessed both at the neurology study

sites and at dedicated pulmonary function facilities during the DLCO visits that were scheduled to take place within 2 weeks before TV3, TV4, TV5, and TV6, and at 4 to 5 weeks after TV6. After implementation of protocol Version 4.0, spirometry assessments were removed from the neurology study sites since the pulmonary function facilities had expertise in spirometry and were performing it in addition to the DLCO assessment. Spirometry was kept at the neurology study sites for Screening and TV1 since those results were needed for eligibility determination and post dose assessments after the first dose, respectively. As part of the procedure at the pulmonary function facilities, a slow vital capacity maneuver was performed first, followed by DLCO, and then spirometry. These assessments were to be performed in an ON state, as reported by the patient to the pulmonary technologist.

Spirometry data collected at pulmonary function facilities were reviewed immediately by a pulmonologist on site for safety signals, and were then sent for review and over-reading by qualified respiratory technologists at the central pulmonary function testing reviewers.

DLCO

Patients underwent DLCO assessments at a dedicated pulmonary function facility after SV2 (CVT-301-naive patients and CVT-301-009 patients), within 2 weeks before TV3, TV4, TV5, and TV6, and at 4 to 5 weeks after TV6. The pulmonary function facilities were certified by a central pulmonary function testing site. The assessments were performed while the patient was in the ON state (as reported by the patient to the pulmonary technician). During the acquisition of these assessments, it was noted whether the attempt fulfilled ATS criteria. Results were summarized for all attempts and, separately, for attempts that fulfilled ATS criteria. Pulmonary function facility technicians performed a slow vital capacity maneuver, followed by DLCO, and then spirometry. The DLCO and slow vital capacity maneuvers were assessed and processed in accordance with ATS/ERS standards. All DLCO data collected at pulmonary function facilities were sent to and reviewed by a central pulmonary function testing reviewer.

Pulmonary Safety Monitoring and Event Adjudication

Pulmonary safety monitoring and event adjudication was established to evaluate changes in pulmonary function data that could potentially indicate patients with pulmonary abnormalities that would not be suitable for participation in the study. Pulmonary safety monitoring and event adjudication processes, in conjunction with review of pulmonary safety by the DSMB, were designed to observe possible trends in pulmonary safety at the patient and study level and to make a distinction between poor pulmonary function testing results because of underlying neuromuscular disease versus underlying pulmonary disease (ie. asthma or COPD). Pulmonary safety monitoring and event adjudication was carried out by a team of pulmonary and respiratory function experts, including a board certified pulmonologist, a registered pulmonary function technologist, registered respiratory therapist and pulmonary function technologist.

Patient Disposition

Table 1. Number of Patients Enrolled and Study Disposition (All Available Population)

	CVT-301 DL1 n (%)	CVT-301 DL2 n (%)	Total n (%)
Screened			346 (100)
Failed Screening ^a			21 (6.1)
Randomized ^a	161	164	325 (93.9)
Ongoing ^b	80 (49.7)	82 (50.0)	162 (49.8)
Completed Study ^b	28 (17.4)	39 (23.8)	67 (20.6)
Withdrawn from Study ^b	53 (32.9)	43 (26.2)	96 (29.5)
Reason for Withdrawal from Study ^c			
Adverse Event	9 (17.0)	10 (23.3)	19 (19.8)
Lack of Efficacy	10 (18.9)	6 (14.0)	16 (16.7)
Protocol Violation	2 (3.8)	0	2 (2.1)
Lost to Follow-up	2 (3.8)	1 (2.3)	3 (3.1)
Other	7 (13.2)	8 (18.6)	15 (15.6)
Withdrawal of Consent by Subject	23 (43.4)	18 (41.9)	41 (42.7)

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa; ITT = Intent-to-Treat.

^a Percentages were based on the number of screened patients.

^b Percentages were based on the number of randomized patients. Please note that this is an interim report.

^c Percentages were based on the number of randomized patients withdrawn from study.

Source: Study CVT-301-400E CSR Table 4, p 67

Of the 346 patients who were screened for the study, 237 (68.5%) were rollover patients from Study-004, 60 (17.3%) were CVT-301 naive patients who were not previously enrolled in CVT-301 studies, 30 (8.7%) were rollover patients from the Observational Cohort in CVT Study-005, 11 (3.2%) were rollover patients from Study-003, and 8 (2.3%) were rollover patients from Study-009.

Altogether, 325 patients (93.9% of the 346 screened) were randomized and 312 patients (96.0%) received at least 1 dose of study drug and were included in the Safety Population. Thirteen patients were randomized but did not receive study drug. A total of 201 (64.4%) of the Safety Population patients were from the United States, 84 (26.9%) from Poland, 11 (3.5%) from Spain, 8 (2.6%) from Canada, and 8 (2.6%) from the Czech Republic.

There were 312 patients in the Safety Population (basis of the pulmonary safety review). At Screening, 294 patients (94.2% of patients in total) had an FEV1 $\geq$ 60% and FEV1/FVC ratio $\geq$ 70%. Screening spirometry and baseline PD disease severity was similar between dose groups. The proportion of patients reported to be current smokers was slightly higher in the 84 mg treatment arm (5.7%) vs. the 60 mg treatment arm (1.3%).

Of the 96 patients withdrawn from the study, 19 patients (19.8%) were withdrawn because of AEs. While there was no observed dose response for AE-related withdrawal overall, pulmonary AEs led to the majority of withdrawals, cough being the most prevalent.

Safety Evaluation

Extent of Exposure

The mean (SD) duration of exposure was 201(113.2) days overall, and was 189 (110.4), and 212 (115.1) days for DL1 (60 mg) and DL2 (84 mg), respectively. The mean duration of exposure is notably less than 52 weeks because of patients remaining active in the ongoing study at the time of the data snapshot.

Dose Modification

Twelve patients (3.8%) overall decreased their dose from 2 to 1 capsule. One of those patients on 60 mg and 1 patient on 84 mg subsequently increased the dose back to 2 capsules. The proportion of patients who decreased their dose was similar in both dose groups.

Deaths

None

Serious Pulmonary Adverse Events

Altogether, 15 (9.8%) patients in the CVT-301 60 mg group and 10 (6.3%) patients in the CVT-84mg group reported a serious TEAE. One (1) patient on CVT-301 60mg had pneumonia and 1 patient had acute respiratory failure. In the 84mg cohort there were no serious pulmonary adverse events noted.

Adverse Events Leading to Study Withdrawal

Table 2. Treatment-Emergent Adverse Events Leading to Study Withdrawal by Preferred Term (Safety Population)

Preferred Term ^a	DL1 (N=153) n (%)	DL2 (N=159) n (%)	Total (N=312) n (%)
Any ^b	8 (5.2)	9 (5.7)	17 (5.4)
Cough	4 (2.6)	2 (1.3)	6 (1.9)
Euphoric mood	1 (0.7)	1 (0.6)	2 (0.6)
CNS lesion	0	1 (0.6)	1 (0.3)
Dyskinesia	0	1 (0.6)	1 (0.3)
Dyspnea	0	1 (0.6)	1 (0.3)
Dystonia	0	1 (0.6)	1 (0.3)
Hallucination	0	1 (0.6)	1 (0.3)
Hallucination, visual	0	1 (0.6)	1 (0.3)
Hyperhidrosis	0	1 (0.6)	1 (0.3)
Intentional drug misuse	0	1 (0.6)	1 (0.3)
Vision blurred	0	1 (0.6)	1 (0.3)
Wheezing	0	1 (0.6)	1 (0.3)
Nasopharyngitis	1 (0.7)	0	1 (0.3)
Rib fracture	1 (0.7)	0	1 (0.3)
Throat irritation	1 (0.7)	0	1 (0.3)

Abbreviations: CNS = Central nervous system; CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa.

Treatment-emergent adverse events were defined as adverse events that started after the patient received the first dose of study drug.

^a Adverse events were coded into system organ class and preferred term using Medical Dictionary for Regulatory Activities version 17.0.

^b The study is ongoing; data are still being reconciled with AEs leading to study drug discontinuation.

Source: Listing 16.2.1 and Listing 16.2.7.1.

Source: Study CVT-301-400E CSR p.100 Table 21

Overall, 17 patients (5.4%) in the Safety Population experienced a TEAE that led to study withdrawal: 8 (5.2%) in the 60 mg group and 9 (5.7%) in the 84 mg group. The only pulmonary TEAEs that led to study withdrawal in more than 1 patient were cough, which occurred in 4 patients (2.6%) in the 60 mg group and 2 patients (1.3%) in the 84 mg group.

Adverse Events leading to Study Drug Discontinuation

Table 3. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ^a	CVT-301 DL1 (N=153)		CVT-301 DL2 (N=159)		Total (N=312)	
	Patients n (%)	Events n	Patients n (%)	Events N	Patients n (%)	Events n
Any ^b	7 (4.6)	7	10 (6.3)	15	17 (5.4)	22
Respiratory, thoracic and mediastinal disorders	5 (3.3)	5	3 (1.9)	4	8 (2.6)	9
Cough	4 (2.6)	4	2 (1.3)	2	6 (1.9)	6
Dyspnoea	0	0	1 (0.6)	1	1 (0.3)	1
Throat irritation	1 (0.7)	1	0	0	1 (0.3)	1
Wheezing	0	0	1 (0.6)	1	1 (0.3)	1
Nervous system disorders	0	0	3 (1.9)	3	3 (1.0)	3
Central nervous system lesion	0	0	1 (0.6)	1	1 (0.3)	1
Dyskinesia	0	0	1 (0.6)	1	1 (0.3)	1
Dystonia	0	0	1 (0.6)	1	1 (0.3)	1
Psychiatric disorders	0	0	2 (1.3)	4	2 (0.6)	4
Euphoric mood	0	0	1 (0.6)	1	1 (0.3)	1
Hallucination	0	0	1 (0.6)	1	1 (0.3)	1
Hallucination, visual	0	0	1 (0.6)	2	1 (0.3)	2
Eye disorders	0	0	1 (0.6)	1	1 (0.3)	1
Vision blurred	0	0	1 (0.6)	1	1 (0.3)	1
General disorders and administration site conditions	0	0	1 (0.6)	1	1 (0.3)	1
Fatigue	0	0	1 (0.6)	1	1 (0.3)	1
Infections and infestations	1 (0.7)	1	0	0	1 (0.3)	1
Nasopharyngitis	1 (0.7)	1	0	0	1 (0.3)	1
Injury, poisoning and procedural complications	1 (0.7)	1	0	0	1 (0.3)	1
Rib Fracture	1 (0.7)	1	0	0	1 (0.3)	1
Skin and subcutaneous tissue disorders	0	0	1 (0.6)	1	1 (0.3)	1
Hyperhidrosis	0	0	1 (0.6)	1	1 (0.3)	1
Surgical and medical procedures	0	0	1 (0.6)	1	1 (0.3)	1
Intentional drug misuse	0	0	1 (0.6)	1	1 (0.3)	1

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa.
Treatment-emergent adverse events were defined as adverse events that started after the patient received the first dose of study drug.

^a Adverse events were coded into system organ class and preferred term using Medical Dictionary for Regulatory Activities version 17.0.

^a Adverse events were coded into system organ class and preferred term using Medical Dictionary for Regulatory Activities version 17.0.

^b The study is ongoing; this data is still being reconciled with the AEs leading to study withdrawal.

Source: Table 14.3.2.13.1.

Source: Study CVT-301-004 Table 22 CSR p. 101

Study drug discontinuations mirrored study withdrawal and revealed no new information.

Table 4. Treatment Emergent Adverse Events Overall Summary (Safety Population)

	CVT-301 DL1 (N=153)		CVT-301 DL2 (N=159)		Total (N=312)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAEs	89 (58.2)	322	97 (61.0)	298	186 (59.6)	620
Serious TEAEs	15 (9.8)	24	10 (6.3)	14	25 (8.0)	38
TEAEs leading to death	0	0	0	0	0	0
TEAEs leading to study withdrawal ^b	8 (5.2)	8	9 (5.7)	13	17 (5.4)	21
TEAEs leading to study drug discontinuation	7 (4.6)	7	10 (6.3)	15	17 (5.4)	22
TEAEs leading to study drug interruption	8 (5.2)	14	12 (7.5)	19	20 (6.4)	33
TEAEs leading to dose reduction	3 (2.0)	3	5 (3.1)	5	8 (2.6)	8
Drug-related TEAEs ^a	40 (26.1)	73	48 (30.2)	90	88 (28.2)	163
Severe TEAEs	15 (9.8)	23	11 (6.9)	18	26 (8.3)	41

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa; TEAE = treatment-emergent adverse event.

A TEAE was defined as an adverse event that started after the patient received the first dose of study drug.

^a Adverse events were considered drug-related if the event was classified as possibly, probably, or definitely related to study drug by investigators.

Source: Study CVT-301-004E CSR table 18 p 92

Adverse Events leading to Study Drug Interruption or Dose Reduction

Overall, 20 patients (6.4%) experienced 33 TEAEs that led to study drug interruption. Treatment-emergent AEs that led to study drug interruption were similar between dose groups. In the CVT-301 60 mg group cough, pneumonia and upper respiratory tract infection led to drug interruption in 1 patient each. In the CVT-301 84mg group nasopharyngitis and bronchitis led to drug interruption in 1 patient each and cough led to interruption in 3 patients.

Overall, 8 patients (2.6%) experienced 8 TEAEs that led to study drug dose reduction (3 patients in the 60mg group and 5 patients in the 84mg group). Of the pulmonary related TEAEs cough led to dose reduction in 1 patient on 84mg, and increased airway secretions led to dose reduction in 1 patient in the 60mg group.

Table 5. Treatment-Emergent Pulmonary Adverse Events (Safety Population)

SOC Preferred Term*	CVT-301 DL1 (N=153)		CVT-301 DL2 (N=159)		Total (N=312)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any	89 (58.2)	322	97 (61.0)	298	186 (59.6)	620
Respiratory, thoracic and mediastinal disorders	34 (22.2)	52	33 (20.8)	50	67 (21.5)	102
Cough	23 (15.0)	25	22 (13.8)	26	45 (14.4)	51
Throat irritation	5 (3.3)	6	4 (2.5)	5	9 (2.9)	11
Oropharyngeal pain	4 (2.6)	4	2 (1.3)	2	6 (1.9)	6
Sputum discoloured	2 (1.3)	2	3 (1.9)	3	5 (1.6)	5
Dyspnoea	3 (2.0)	3	1 (0.6)	1	4 (1.3)	4
Dysphonia	1 (0.7)	1	2 (1.3)	2	3 (1.0)	3
Nasal discharge discolouration	0	0	3 (1.9)	3	3 (1.0)	3
Dyspnoea exertional	1 (0.7)	1	1 (0.6)	1	2 (0.6)	2
Increased upper airway secretion	2 (1.3)	2	0	0	2 (0.6)	2
Nasal congestion	1 (0.7)	1	1 (0.6)	1	2 (0.6)	2
Sleep apnoea syndrome	0	0	2 (1.3)	2	2 (0.6)	2
Upper respiratory tract irritation	1 (0.7)	1	1 (0.6)	1	2 (0.6)	2
Wheezing	1 (0.7)	1	1 (0.6)	1	2 (0.6)	2
Acute respiratory failure	1 (0.7)	3	0	0	1 (0.3)	3
Epistaxis	0	0	1 (0.6)	1	1 (0.3)	1
Hiccups	1 (0.7)	1	0	0	1 (0.3)	1
Respiratory tract congestion	1 (0.7)	1	0	0	1 (0.3)	1
Rhinitis allergic	0	0	1 (0.6)	1	1 (0.3)	1
Infections and infestations	29 (19.0)	44	30 (18.9)	36	59 (18.9)	80
Pneumonia	2 (1.3)	2	2 (1.3)	2	4 (1.3)	4
Pneumonia mycoplasmal	0	0	1 (0.6)	1	1 (0.3)	1

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; DL = dose level; LD = levodopa.
Treatment-emergent adverse events were defined as adverse events that started after the patient received the first dose of study drug.

Source: CVT-301-004E, CSR Table 24 p 103

The most common pulmonary adverse events in Study 004E were cough, throat irritation, oropharyngeal pain, sputum discolored, dyspnea, and dysphonia. The most common adverse event (AE) was cough occurring in 23 (35%) of patients on 60mg and 22 (13%) of patients on 84mg. Of the 51 total TEAEs of cough 31 were mild, 14 moderate and 6 were severe. Throat irritation occurred in 5 (3%) on 60mg and 4 (2%) on 84mg. Discolored sputum occurred in 2 patients on 60 mg and 3 patients on 84 mg.

Table 6. Spirometry Change from Baseline at Treatment Visits 3-6 and at Follow-Up (Safety Population, Pulmonary Function Facility)

Parameter	Visit	Statistic	CVT-301 DL1	CVT-301 DL2	Total
Change from Baseline (L)					
FEV1	TV3 (Week 12)	n	138	146	284
		Mean (SD)	-0.066 (0.2317)	-0.076 (0.2050)	-0.071 (0.2181)
	TV4 (Week 24)	n	113	131	244
		Mean (SD)	-0.056 (0.2023)	-0.054 (0.2141)	-0.055 (0.2083)
	TV5 (Week 36)	n	78	93	171
		Mean (SD)	-0.124 (0.1905)	-0.048 (0.2073)	-0.083 (0.2028)
	TV6 (Week 52)	n	50	58	108
		Mean (SD)	-0.163 (0.2174)	-0.124 (0.2544)	-0.142 (0.2377)
	FU	n	43	50	93
		Mean (SD)	-0.185 (0.3023)	-0.068 (0.2743)	-0.122 (0.2920)

Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg; DL = dose level; FEV1 = forced expiratory volume in 1 second; FU = follow-up; SD = standard deviation; TV = Treatment Visit. Screening is the latest assessment during the Screening Period. Baseline is defined as the TV1 Arrival value. If the TV1 Arrival value was missing, the last available value in ON state before the first dose of study drug was used.

Source: Study CVT-301-004E CSR, table 30 pg 114

The mean change from baseline in FEV1 at Week 52 for both dose groups was -0.163L and -0.124L, respectively. The magnitude of the change from baseline was inconsistent/variable over time (including at follow up), but in general did not show a dose response. Further interpretation is limited due to the lack of a control group.

Spirometry was also assessed for the subgroups of patients who were treated in Study CVT-301-004 with CVT-301 versus those treated with placebo compared to CVT-301-naïve patients. In rollover patients from study CVT-301-004, the decrease of the LS mean change of FEV1 from baseline was larger at all visits for the patients who had received CV-301 in the earlier study than for patients who had received placebo. The differences between the 2 groups were statically significant ($p < 0.05$) at TV3, TV4, and TV6. The magnitude of the LS mean change from baseline increased over time and was highest at TV6, when it was -0.202 L (SE 0.0338) for the patients who had received CVT-301 and -0.094 L (SE 0.0512) for patients who had received placebo. The baseline values of FEV1 for these two groups was different (the CVT-301 treated patients baseline was from the start of study CVT-301-004 and the baseline of the placebo treated patients was from the end of the 12 week study). Given that study CVT-301-004E had no control group it is hard to interpret the influence the time difference between baseline determination had on the results. In addition, the decreasing numbers of patients in the latter visits of this Study 004E makes interpretation of data from those visits difficult and unreliable.

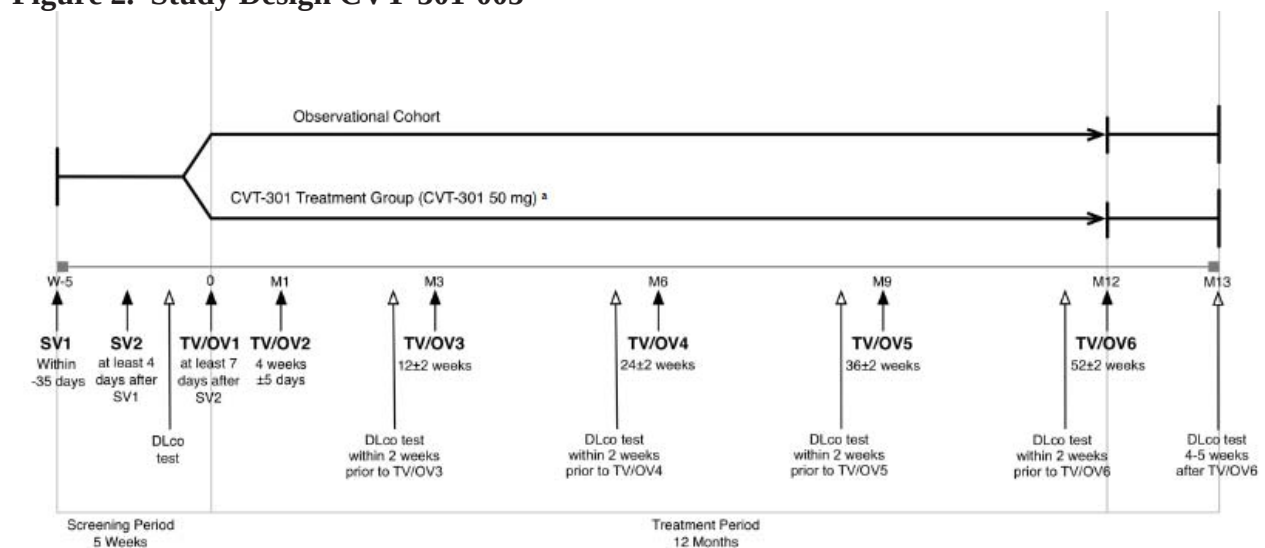
2. CVT-301- 005

Study Design

This was a 12-month, open-label, randomized, multicenter study that evaluated the safety and effects of inhaled CVT-301 84mg in patients with PD experiencing motor response fluctuations (off phenomena) and included a concurrent observational cohort of patients with PD managed using standard-of-care treatments. Patients assigned to the observational cohort did not receive study drug or inhaled placebo. The primary objective was assessed by spirometry (FEV1, FVC, and FEV1/FVC ratio) over a 12-month period. A total of 408 patients were enrolled and assigned to CVT-301 84 mg (n=278) or the observational cohort (n=130).

The study included a Screening Period of up to 35 days and a Treatment Period of approximately 12 months (52 $\pm$ 2 weeks) with 6 TVs or Observation Visits (OV) plus an additional follow-up at a pulmonary function facility 4 to 5 weeks after the last Treatment or Observation Visit. Planned TVs/OVs occurred at pre-dose/baseline, and at approximately 1, 3, 6, 9, and 12 months. Planned TVs/OVs occurred at pre-dose/baseline, and at approximately 1, 3, 6, 9, and 12 months.

Figure 2. Study Design CVT-301-005



Abbreviations: DLco = diffusion capacity of the lungs for carbon monoxide; M = month; SV = Screening Visit; TV/OV = Treatment Visit/Observation Visit; W = week.

^aCVT-301 50 mg refers to the fine particle dose. Spirometry was assessed at the pulmonary function facilities at the same time as the DLco tests.

Source: Study CVT-301-005 CSR Figure 1 pg 27

Pertinent Pulmonary Inclusion Criteria

- Male or female aged 30-85 years of age
- If a current smoker, was able to comply with the following guidelines: agrees not to smoke for the entire clinic visit days (including screening visits, in-clinic treatment visits, and follow-up visit) until completion of all study procedures.
- If the patient is a current or former smoker, has no history of, nor has ever been treated for any smoking-related pulmonary condition (e.g., chronic bronchitis, emphysema,

chronic obstructive pulmonary disease [COPD]) or asthma, and has no evidence of obstructive lung disease by spirometry assessment. Patient must agree to abstain from smoking on the day of each in-clinic visit from waking through completion of all assessments for that visit day.

- Has a screening FEV1 $\geq$ 50% of predicted for race, age, sex, and height, and FEV1/FVC ratio $>60\%$, in the ON state at Screening.

Pertinent Pulmonary Exclusion Criteria

- Patients who had prior exposure to CVT-301 (not applicable to early versions of the protocol where patients from designated other CVT-301 studies [CVT-301-002 and CVT-301-003] could have been enrolled).
- Has a history of COPD, asthma, or other chronic respiratory diseases within the last 5 years
- Has any contraindication to performing routine spirometry

Smoking Restrictions (listed under Prohibited Medications in the Study Report):

Smokers had to agree to and had to be able to abstain from smoking on the day of each in-clinic visit while in-clinic through completion of all assessments for that visit day (including Screening Visits and in-clinic treatment visits).

Spirometry

Pulmonary function was measured by spirometry using the guideline specified by the Third National Health and Nutrition Examination Survey III (Hankinson 1999). Spirometry assessments were done within 2 weeks prior to the 3-, 6-, 9-, and 12 month study visits and 4 to 5 weeks following completion of TV/OV6. The patient's motor state at the time of each spirometry assessment was recorded. Pulmonary function testing was performed at neurology study sites and at dedicated pulmonary function facilities. Spirometry equipment was provided to each neurology study site to perform the assessments. Spirometry was performed by staff at neurology study sites that were trained and qualified by a central spirometry laboratory and spirometry performed at the pulmonary function facilities were performed by staff that were certified by a central pulmonary function testing reviewer. Quality over-read of all spirometry efforts was done based on acceptability and repeatability metrics in accordance with ATS criteria recommendations (Miller 2005). Spirometry at both neurology study sites and pulmonary function facilities was performed with the goal of meeting ATS acceptability and repeatability criteria. After Screening, if no acceptable efforts were obtained, the values from the effort with the highest summed FEV1 and FVC were reported.

Screening

Spirometry was performed at the neurology study sites at Screening. At SV1, spirometry assessments were done both while the patient was in the ON and OFF states. Pulmonary safety monitoring and event adjudication was established to identify pulmonary function data to indicate that the patient may have pulmonary abnormalities that would not be suitable for inclusion in the study. A pulmonologist reviewed the spirometry tracings/morphology of any

patient with an FEV1 that was $\geq 50\%$ to $< 60\%$ of predicted or an FEV1/FVC ratio that was $> 60\%$ to $< 70\%$ at Screening to identify patients with possible abnormal spirometry outside of what would be expected with PD to determine eligibility. Patients with an FEV1/FVC ratio that was $> 60\%$ to $< 70\%$ at Screening completed spirometry before and after the administration of a bronchodilator in a pulmonary function facility. The results of the bronchodilator challenge were reviewed before potential randomization.

Acute Pulmonary Safety

In conjunction with the Drug Safety Monitoring Board (DSMB), pulmonary safety monitoring and event adjudication processes were designed to identify trends in pulmonary safety at the patient and study level. At the time of each spirometry assessment, staff recorded the patient's motor state. If within the first 60 minutes after inhalation, the patient's spirometry assessment showed either of the following, the site followed the Spirometry Alert and Review Process: a decrease in FEV1 $\geq 20\%$ AND a decrease in FEV1 by 200 mL compared with pre-dose results, and/or a reduction in the FEV1/FVC ratio to $< 60\%$. If either criteria were met, the patient was not sent home with study drug and the following procedures were followed: (1) any emergent medical conditions were managed as needed; (2a) a Spirometry Alert and Review Worksheet was completed, including documentation of medical assessments and the presence/absence of pulmonary and any other signs or symptoms were recorded, and the worksheet was transmitted to prespecified personnel; (2b) the spirometry assessments were immediately transmitted to the Spirometry Core Laboratory; and (3) all other TV1 safety assessments were completed. The site ensured that the patient was clinically stable before leaving the site. The medical monitor and Acorda determined whether or not the patient could continue study participation.

Chronic Pulmonary Safety

Until protocol amendment Version 4.0, spirometry was assessed both at the neurology study sites and at dedicated pulmonary function facilities during the DLCO visits that were scheduled to take place within 2 weeks before TV3, TV4, TV5, and TV6, and at 4 to 5 weeks after TV6. After implementation of protocol Version 4.0, spirometry assessments were removed from the neurology study sites since the pulmonary function facilities had expertise in spirometry and were performing it in addition to the DLCO assessment. Spirometry was kept at the neurology study sites for Screening and TV1 since those results were needed for eligibility determination and post dose assessments after the first dose, respectively.

Spirometry data collected at pulmonary function facilities were reviewed immediately by a pulmonologist on site for safety signals, and were then sent for review and over-reading by qualified respiratory technologists at the central pulmonary function testing reviewer site.

Predefined changes that were specified in the pulmonary safety charter for findings at any Treatment Visit or Observation Visit that were subject to additional review and adjudication included (1) a change from Baseline value in FEV1 or FVC $\geq 15\%$; or (2) a change from Baseline value in DLco $\geq 20\%$; or (3) a drop below 60% of the predicted value for DLco. Spirometry and DLco results were manually evaluated to identify patients who met any of these criteria.

Pulmonary Safety Monitoring and Event Adjudication

Pulmonary safety monitoring and event adjudication processes, in conjunction with review of pulmonary safety by the DSMB, were designed to observe possible trends in pulmonary safety at the patient and study level and to make a distinction between poor pulmonary function testing results because of underlying neuromuscular disease versus underlying pulmonary disease. Pulmonary safety monitoring and event adjudication was carried out by a team of pulmonary and respiratory function experts, including a board certified pulmonologist, a registered pulmonary function technologist, registered respiratory therapist and pulmonary function technologist.

Reviewer's comment: A total of 131 patients (32.9%) had a reduction from Baseline in FEV1, FVC, or DLco that met the pre-specified alert criteria at a Treatment or Observation Visit and underwent pulmonary adjudication. The majority of these cases had spirometry changes that were proportional drops in FEV1 and FVC without a drop in FEV/FVC which is not likely due to airway obstruction but more indicative of loss of volume or inadequate inhalation.

Patient Disposition

Of 513 patients screened for entry into the study 105 patients (20.5%) failed Screening. Reasons for failure related to pulmonary criteria included inability to perform a spirometry maneuver or not meeting the FEV1 and FEV1/FVC criteria, having COPD, asthma or other chronic respiratory disease (7 patients, 1.4%). A total of 408 (79.5%) of the 513 patients screened were randomly assigned to the CVT-301 (n=278) or the observational cohort (n=130). Of the 408 patients, 398 received at least one dose of inhaled CVT-301 or came in for OV1 and were included in the Safety Population. The majority of the patients in the Safety population were enrolled in Poland and Romania.

Table 7. Number of Patients Enrolled and Study Termination (All Available Population)

	Obs Cohort n (%)	CVT-301 Total n (%)	Overall n (%)
Screened			513
Failed Screening ^a			105 (20.5)
Randomized ^a	130	278	408 (79.5)
Completed Study ^b	106 (81.5)	204 (73.4)	310 (76.0)
Withdrawn from Study ^b	24 (18.5)	74 (26.6)	98 (24.0)
Reason for Withdrawal from Study ^c			
Adverse Event ^d	0	28 (37.8)	28 (28.6)
Lack of Efficacy	0	8 (10.8)	8 (8.2)
Protocol Violation	0	1 (1.4)	1 (1.0)
Lost to Follow-up	0	2 (2.7)	2 (2.0)
Other	3 (12.5)	5 (6.8)	8 (8.2)
Patient Withdrew Consent	21 (87.5)	30 (40.5)	51 (52.0)

Abbreviations: Obs = Observational.

Notes: The CVT-301 Total column includes 3 patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and CVT-301 Naïve patients combined.

^a Percentages are based on the number of screened patients.

^b Percentages are based on the number of randomly assigned patients.

^c Percentages are based on the number of randomly assigned patients withdrawn from study.

^d Three patients who did not receive study drug, and 1 patient with a pre-existing condition of chronic lymphocytic leukemia are included in the 28 patients who withdrew due to an adverse event.

Source Study CVT-301-005 CSR Table 3 pg 61

As shown in Table 7, of the 408 randomized patients, n=74 (27%) withdrew from the study in the CVT-301 group vs. n=24 (19%) in the observational cohort (OC). The two most common reasons for withdrawal from the study were adverse events (n=28 (38%), CVT-301 vs. 0 OC) and withdrawal of consent (n=30 (41%) CVT-301 vs. n=21 (88%) OC).

Safety Evaluation

Extent of Exposure

The mean (SD) duration of exposure was 308.9 (113.21) days for patients in the CVT-301 treatment group. A total of 204 patients in the CVT-301 treatment group completed the 12-month study. The mean (SD) average daily doses taken was 2.33 (0.938) doses overall for patients in the CVT-301 treatment group. A total of 183 patients (67.5%) used 4 doses per day at least once and 94 patients (34.7%) used 5 doses per day at least once.

Dose Modification

Eleven patients (4.1%) decreased the study drug dose: 5 patients (1.8%) went from 2 capsules to 1, 4 (1.5%) went from 2 capsules to 1 and subsequently to 60mg. Five of these patients (1.8%) later increased their dose of study drug back to either 2 capsules (84 mg) or 60 mg.

Deaths

One patient in the CVT-301 treatment group experienced an SAE that led to death. The event was a hypoxic-anoxic encephalopathy (hypoxic-ischemic encephalopathy) in a subject on CVT-301 who was using his home pool and drowned.

Nonfatal Serious Pulmonary Adverse Events

Overall, 55 patients (13%) patients experienced a treatment-emergent SAE: 42 patients (15.5%) in the CVT-301 treatment group and 13 patients (10.2%) in the observational cohort. Pulmonary SAEs reported in single patients in the CVT-301 group included respiratory tract infection, anoxia, bronchial hyperreactivity, pulmonary embolism, respiratory failure, and restrictive pulmonary disease. No pulmonary SAEs were experienced by more than one patient.

Table 8. Treatment-emergent Adverse Events Overall Summary (Safety Population)

	Obs Cohort (N = 127)		CVT-301 Total (N = 271)		Overall (N = 398)	
	Patients n (%)	E n	Patients n (%)	E n	Patients n (%)	E n
Any TEAEs	73 (57.5)	214	192 (70.8)	654	265 (66.6)	868
Serious TEAEs	13 (10.2)	18	42 (15.5)	61	55 (13.8)	79
TEAEs Leading to Death	0	0	1 (0.4)	1	1 (0.3)	1
TEAEs Leading to Study Withdrawal ^a	0	0	24 (8.9)	35	24 (6.0)	35
TEAEs Leading to Study Drug Discontinuation	0	0	22 (8.1)	50	22 (5.5)	50
TEAEs Leading to Study Drug Interruption	0	0	33 (12.2)	51	33 (8.3)	51
TEAEs Leading to Dose Reduction	0	0	8 (3.0)	9	8 (2.0)	9
Drug-related TEAEs ^b	0	0	102 (37.6)	209	102 (25.6)	209
Severe TEAEs	9 (7.1)	14	36 (13.3)	57	45 (11.3)	71

Abbreviations: E = event(s); Obs = Observational; TEAE = treatment-emergent adverse event.

Notes: The CVT-301 Total column includes 3 patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and CVT-301 Naïve patients combined.

A TEAE was defined as an adverse event that started on or after the first dose of study drug for patients in the CVT-301 treatment group or on or after the date of Observation Visit 1 for patients in the observational cohort.

^a Three patients who did not receive study drug, and 1 patient with a pre-existing condition of chronic lymphocytic leukemia are NOT included in the 24 patients who withdrew from the study due to an adverse event.

^b Adverse events were considered drug-related if the event was classified as possibly, probably, or definitely related to study drug by the Investigators.

Source: Study CVT-301-005 CSR Table 19 pg 96

Table 9. Treatment-emergent Adverse Events Leading to Study Withdrawal by Preferred Term (Safety Population)

Preferred Term ^a	(N = 127)		(N = 271)		(N = 398)	
	Patients n (%)	E n	Patients n (%)	E n	Patients n (%)	E n
Any TEAEs	0	0	24 (8.9)	35	24 (6.0)	35
Cough	0	0	3 (1.1)	3	3 (0.8)	3
Bronchitis	0	0	2 (0.7)	2	2 (0.5)	2
Hallucination	0	0	2 (0.7)	2	2 (0.5)	2
Anoxia	0	0	1 (0.4)	1	1 (0.3)	1
Cerebrovascular accident	0	0	1 (0.4)	1	1 (0.4)	1
Dehydration	0	0	1 (0.4)	1	1 (0.3)	1
Dopamine dysregulation syndrome	0	0	1 (0.4)	1	1 (0.3)	1
Drug intolerance	0	0	1 (0.4)	1	1 (0.3)	1
Dry mouth	0	0	1 (0.4)	1	1 (0.3)	1
Dyskinesia	0	0	1 (0.4)	1	1 (0.3)	1
<i>Escherichia</i> urinary tract infection	0	0	1 (0.4)	1	1 (0.3)	1
Flushing	0	0	1 (0.4)	1	1 (0.3)	1
Hip fracture	0	0	1 (0.4)	1	1 (0.3)	1
Hypertension	0	0	1 (0.4)	1	1 (0.3)	1
Metastases to central nervous system	0	0	1 (0.4)	1	1 (0.3)	1
Nephrolithiasis	0	0	1 (0.4)	1	1 (0.3)	1
Nasal congestion	0	0	1 (0.4)	1	1 (0.3)	1
Nausea	0	0	1 (0.4)	1	1 (0.3)	1
Occipital neuralgia	0	0	1 (0.4)	1	1 (0.3)	1
Orthostatic hypotension	0	0	1 (0.4)	1	1 (0.3)	1
Parkinsonism	0	0	1 (0.4)	1	1 (0.3)	1
Pulmonary embolism	0	0	1 (0.4)	1	1 (0.3)	1
Retinal detachment	0	0	1 (0.4)	1	1 (0.3)	1
Rhabdomyolysis	0	0	1 (0.4)	1	1 (0.3)	1
Salivary hypersecretion	0	0	1 (0.4)	1	1 (0.3)	1
Spondylitis	0	0	1 (0.4)	1	1 (0.4)	1
Syncope	0	0	1 (0.4)	1	1 (0.3)	1
Tachycardia	0	0	1 (0.4)	1	1 (0.3)	1
Throat irritation	0	0	1 (0.4)	1	1 (0.3)	1
Upper respiratory tract irritation	0	0	1 (0.4)	1	1 (0.3)	1
Vision blurred	0	0	1 (0.4)	1	1 (0.3)	1

Abbreviations: E = event(s); Obs = Observational; TEAE = treatment-emergent adverse event.

Notes: The CVT-301 Total column includes 3 patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and CVT-301 Naïve patients combined.

A TEAE was defined as an adverse event that started on or after the first dose of study drug for patients in the CVT-301 treatment group or on or after the date of Observation Visit 1 for patients in the observational cohort.

Source: Study CVT-301-005 CSR Table 23 pg 106

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As shown in Table 8, no patient in the observational cohort withdrew from the study due to adverse events. In the CVT-301 84 mg treatment group 24 (8.9%) patients experienced 35 events leading to withdrawal. As shown in Table 9, pulmonary adverse events that led to

withdrawal were cough in 3(1.1%) of patients, bronchitis in 2 (0.7%) patients, anoxia, nasal congestion, pulmonary embolism, throat irritation, and upper respiratory tract infection led to withdrawal in 1 patient (0.4%) each.

Table 10. Pulmonary-associated Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ^a	Obs Cohort (N = 127)		CVT-301 Total (N = 271)		Overall (N = 398)	
	Patients n (%)	E n	Patients n (%)	E n	Patients n (%)	E n
Respiratory, thoracic and mediastinal disorders	3 (2.4)	3	62 (22.9)	97	65 (16.3)	100
Cough	1 (0.8)	1	36 (13.3)	43	37 (9.3)	44
Sputum discoloured	0	0	9 (3.3)	11	9 (2.3)	11
Throat irritation	0	0	9 (3.3)	10	9 (2.3)	10
Oropharyngeal pain	0	0	5 (1.8)	7	5 (1.3)	7
Dry throat	0	0	3 (1.1)	3	3 (0.8)	3
Dyspnoea	0	0	3 (1.1)	3	3 (0.8)	3
Nasal congestion	0	0	2 (0.7)	2	2 (0.5)	2
Nasal discharge discolouration	0	0	2 (0.7)	2	2 (0.5)	2
Nasal dryness	0	0	2 (0.7)	2	2 (0.5)	2
Productive cough	0	0	2 (0.7)	2	2 (0.5)	2
Anoxia	0	0	1 (0.4)	1	1 (0.3)	1
Aspiration	0	0	1 (0.4)	1	1 (0.3)	1
Bronchial hyperreactivity	0	0	1 (0.4)	2	1 (0.3)	2
Dyspnoea exertional	0	0	1 (0.4)	1	1 (0.3)	1
Epistaxis	0	0	1 (0.4)	1	1 (0.3)	1
Lung disorder	1 (0.8)	1	0	0	1 (0.3)	1
Nasal septum disorder	0	0	1 (0.4)	1	1 (0.3)	1
Pulmonary embolism	0	0	1 (0.4)	1	1 (0.3)	1
Respiratory failure	0	0	1 (0.4)	1	1 (0.3)	1
Restrictive pulmonary disease	0	0	1 (0.4)	1	1 (0.3)	1
Rhinitis allergic	1 (0.8)	1	0	0	1 (0.3)	1
Rhinorrhoea	0	0	1 (0.4)	1	1 (0.3)	1
Upper respiratory tract irritation	0	0	1 (0.4)	1	1 (0.3)	1
Infections and infestations	27 (21.3)	35	67 (24.7)	96	94 (23.6)	131
Bronchitis	4 (3.1)	6	7 (2.6)	7	11 (2.8)	13
Respiratory tract infection	1 (0.8)	1	4 (1.5)	4	5 (1.3)	5
Pneumonia	2 (1.6)	2	2 (0.7)	2	4 (1.0)	4
Respiratory tract infection viral	1 (0.8)	1	1 (0.4)	1	2 (0.5)	2

Abbreviations: E = event(s); Obs = Observational; TEAE = treatment-emergent adverse event.

Notes: The CVT-301 Total column includes 3 patients who were previously enrolled in the CVT-301-002 or CVT-301-003 studies and CVT-301 Naïve patients combined.

A TEAE was defined as an adverse event that started on or after the first dose of study drug for patients in the CVT-301 treatment group or on or after the date of Observation Visit 1 for patients in the observational cohort.

^a Adverse events were coded into system organ class and preferred term using MedDRA version 19.1.

Source: Study CVT-301-005 CSR Table 26 pg 111

The most frequently reported pulmonary TEAEs in the CVT-301 treatment group and occurring with a greater frequency than in the observational cohort were: cough (13% vs. 0.8%), sputum discolored (3.3% vs. 0%), and throat irritation (3.3% vs. 0%).

Most TEAEs of cough started within the first 30 days of CVT-301 treatment (for 28 of 36 patients reporting cough), and most coughs reported in the CVT-301 treatment group were reported as mild in intensity (38 of 43 events). One 1 TEAE of cough was reported as severe and CVT-301 was discontinued.

Spirometry Data

In general, the percentage of patients experiencing a change of -10% to < 10% from Baseline in FEV1, FVC, and FEV1/FVC ratio was similar when comparing results from the pulmonary function facilities and the neurology study sites. However, there appeared to be slightly more variation in the data from the neurology study sites. Therefore, this review focuses on the results obtained from the pulmonary function facilities. This review also focuses on the FEV1 findings, noting that FVC and DLCO showed similar findings.

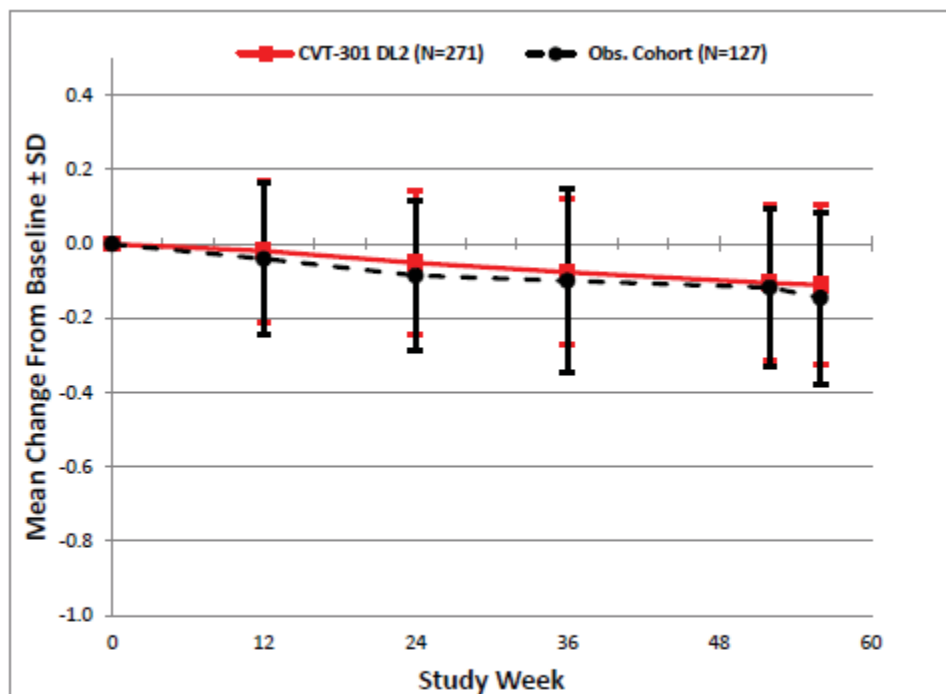
The mean change from baseline in FEV1 is shown by visit in Table 11 and Figure 3 below.

Table 11. Mean Change from Baseline FEV1(L) by Visit – (Safety Population)

Treatment Visit	Observational Cohort change (SD) N=127	CVT-301 Cohort change (SD) N=268	LS mean differences (95% CI)
3	-0.040 (0.2039)	-0.019 (0.1909)	0.022 (-0.022, 0.063)
4	-0.085 (0.2023)	-0.051 (0.1948)	0.033 (-0.010, 0.077)
5	-0.099 (0.2462)	-0.076 (0.1971)	0.022 (-0.027, 0.071)
6	-0.117 (0.2136)	-0.105 (0.2094)	0.002 (-0.046, 0.050)
Follow-up	-0.145 (0.2314)	-0.110 (0.2136)	

Table 14.3.4.5.1.1, pg. 1935, CSR Study 005.

Figure 3. Mean Change from Baseline in FEV1 (L) (Pulmonary Function Facilities)



Abbreviations: FEV1 = forced expiratory volume in 1 second; Obs. = observational; SD = standard deviation.

Source: Table 14.3.4.5.1.1.

Source: Study CVT-301-005 CSR Figure 5 pg 124

The mean values for FEV1 at Baseline were similar between the treatment arms (2.84 L for the observational cohort and 2.84 L for the CVT-301 treatment group). The change from Baseline for FEV1 was compared between the CVT-301 treatment group and the observational cohort. The LS mean differences (95% CI) were 0.021 (-0.022, 0.063) at TV3/OV3 (Week 12), 0.033 (-0.010, 0.077) at TV4/OV4 (Week 24), 0.022 (-0.027, 0.071) at TV5/OV5 (Week 36), and 0.002 (-0.046, 0.050) at TV6/OV6 (Week 52); none of these differences were clinically or statistically significant.

These findings were confirmed by multiple sensitivity analyses, including an Mixed Model for Repeated Measurements Analysis (MMRM).

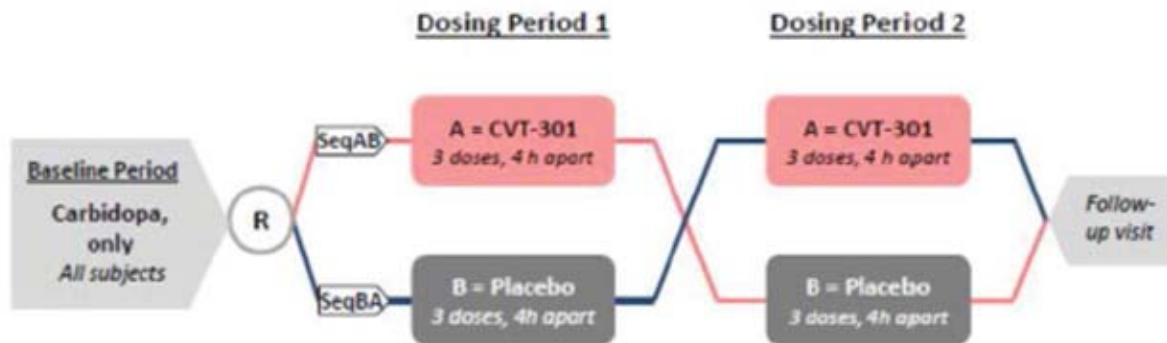
3. CVT-301-008: Asthma Study

Study Design

This was a double-blind, randomized, multiple dose, placebo-controlled, 2-period crossover study investigating the safety and PK of inhaled CVT-301 84-mg compared to placebo in 26 asthmatic patients (without Parkinson's disease). Subjects received 3 doses of CVT-301 (providing a total of 252 mg of levodopa) and 3 doses of placebo in 2 dosing periods separated by a 1-day washout period.

The study included a 26-day screening period, a 1-week clinic period where all subjects were domiciled, and a follow-up visit 1 week after discharge. Each subject received 3 inhaled doses of CVT-301 84 mg administered approximately 4 hours apart and the same regimen with a matching placebo inhalation powder. Carbido[®] was administered orally as a 50mg dose every 8 hours throughout the day during the study. Spirometry was performed within 1.5 hours prior to the first dose and at 15 and 30 minutes, and 1, 4 (before second dose) 4.25, 4.5, 5 (before third dose) 8.25, 8.5, 9, 12, and 24 hours after the first dose.

Figure 4. Study Design CVT-301-008



Study Population

Pertinent Pulmonary Inclusion Criteria

- Non-smoker (past 12 months or < 10 pack years) aged 25-65 years (prior smokers were included)
- Screening FEV1 $\geq 60\%$ of predicted and FEV1/FVC ratio $\geq 70\%$
- Diagnosis of asthma on a stable regimen of asthma medications for at least 30 days

Pertinent Pulmonary Exclusion Criteria

- Long acting bronchodilators within 12 hours and short acting bronchodilators within 4 hours
- Unscheduled or urgent visits to any medical facility for asthma related problems within 8 weeks prior to the screening visit
- More than 2 hospitalizations or emergency room visits, or more than 3 courses of systemic steroids in the past 12 months or 1 course within 8 weeks of the screening visit for respiratory illness
- History of COPD requiring oral or inhaled medical therapy within the last 3 years
- History of intubation or intensive care unit admission within the last 5 years

Screening

There were 38 subjects screened and 12 failed screening based on the Inclusion Exclusion criteria. Of the 26 who were randomized, 1 subject did not continue due to insufficient venous access. 25 subjects completed the study.

Safety Evaluation

Deaths, SAEs, and AEs Leading to Study Withdrawal

There were no deaths, serious adverse events or TEAEs that led to subject withdrawal, dose reduction or interruption.

Adverse Events

Overall, adverse events were reported more frequently in patients receiving CVT-301 vs. placebo (64% vs. 16%). Cough was the most frequent respiratory AE occurring in 15 (60%) of CVT-301 treated patients. 48% of subjects reported 23 TEAEs of cough that were moderate in intensity, and 12% of subjects reported a total of 5 TEAEs that were mild in intensity. Cough occurred immediately after the dose of CVT-301 and was self-limited. There were no reports of cough following administration of placebo.

Spirometry

Categorical Changes in FEV1

Ten (10) of 25 subjects who received CVT-301 had time-matched reductions in FEV1 or that were >15%; however, 4 of these subjects also had similar reductions following inhalation of placebo. There were no rescue medications administered. These reductions in FEV1 were self-limited and no rescue medications were administered. These subjects are outlined in Table 12 below.

Reviewer's comment: While individual patients appeared to have reductions in FEV1 > 12% which would meet the criteria of bronchial hyperresponsiveness, the strength of the evidence that this is due to drug is limited by the fact that these patients also had similar reductions in response to placebo. Further, the patients were asymptomatic and did not require any rescue medications.

Table 12. Subjects with Reductions from Predose and/or Time-matched Reductions from Baseline for FEV1 or FEV1/FVC

Subject	Age (Years)	Sex	Smoking Status ^a	Time-matched % Reductions from Baseline for FEV ₁ or FEV ₁ /FVC that were >15% ^b	% Reductions From Predose for FEV ₁ or FEV ₁ /FVC that were >15% ^b	Asthma Medications
(b) (6)	51	Female	Never-smoker	Yes (CVT-301)	Yes (CVT-301)	Seretide® 250/50 µg BID Procaterol hydrochloride 180 µg PRN
	51	Male	Never-smoker	Yes (CVT-301)	Yes (CVT-301)	Salbutamol sulfate 180 µg PRN
	36	Female	Never-smoker	Yes (CVT-301)	No	Fluticasone propionate 180 µg PRN
	62	Female	Ex-smoker	Yes (CVT-301 and placebo)	Yes (CVT-301 and placebo)	Salbutamol sulfate 180 µg PRN
	38	Male	Never-smoker	Yes (CVT-301)	No	Salbutamol sulfate 180 µg PRN
	41	Female	Never-smoker	Yes (CVT-301)	Yes (CVT-301)	Budesonide + formoterol fumarate BID Procaterol hydrochloride 180 µg PRN
	52	Female	Never-smoker	Yes (CVT-301 and placebo)	Yes (CVT-301 and placebo)	Salbutamol sulfate 180 µg PRN
	49	Female	Ex-smoker	Yes (CVT-301)	Yes (CVT-301)	Salbutamol sulfate 180 µg PRN
	28	Female	Never-smoker	Yes (CVT-301 and placebo)	Yes (CVT-301 and placebo)	Seretide® 250/50 µg BID Salbutamol sulfate 180 µg PRN
	46	Male	Ex-smoker	Yes (CVT-301 and placebo)	Yes (CVT-301)	Salbutamol sulfate 180 µg PRN

References: Listing 16.2.4-5, Listing 16.2.8-1, Listing 16.2.8-8, Listing 16.2.8-9, Figure 16.2.8-8 and Figure 16.2.8-9.

Abbreviations: BID = twice daily; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; PRN = as needed.

^a No active smokers were enrolled into this study.

^b Data in parentheses indicate the treatment administered during the period in which the >15% reduction was observed.

Source: Study CVT-008 CSR Table 13 pg 58

Mean Changes in FEV1(L)

Table 13 shows the mean changes in FEV1 by time point averaged over both periods over 24 hours for both the placebo and CVT-301 treatment groups. The change from baseline is included in parentheses next to the mean value for each time point. In reviewing the data, there was no appreciable bronchospasm with administration of placebo. The maximum mean decreases in FEV1 in patients treated with CVT-301 84 mg was 169 cc at 15 minutes and 182 cc at 4 hr and 15 minutes. All subjects returned to baseline without rescue medications.

Reviewer's comment: The American Thoracic Society defines bronchial hyperresponsiveness as >12% and 200 mL reduction; the mean absolute FEV1 decline does not meet this criteria.

Table 13. Mean Changes in FEV1 (L) Averaged Over All Periods

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 13 of 96)

CVT-301-008

Study Population: Safety

Parameter: Forced Expiratory Volume in 1 Second (L)

Treatment	Statistic	Timepoint						
		Predose	15 min	30 min	1 h	4 h	4.25 h	4.5 h
Placebo	n	24 [23]	25 [25]	23 [21]	25 [25]	25 [25]	25 [23]	24 [23]
	Mean	2.380 [0.019]	2.343 [-0.014]	2.354 [-0.041]	2.361 [-0.034]	2.338 [-0.070]	2.360 [-0.069]	2.353 [-0.054]
	SD	0.6086 [0.1653]	0.6037 [0.1675]	0.6130 [0.1330]	0.6029 [0.1675]	0.6414 [0.1849]	0.6142 [0.1374]	0.6259 [0.1460]
	SE	0.1242 [0.0345]	0.1207 [0.0335]	0.1278 [0.0290]	0.1206 [0.0335]	0.1283 [0.0370]	0.1228 [0.0286]	0.1278 [0.0304]
	Median	2.320 [0.010]	2.290 [-0.040]	2.310 [-0.060]	2.380 [-0.020]	2.300 [-0.030]	2.350 [-0.040]	2.230 [-0.070]
	Min	1.50 [-0.21]	1.43 [-0.37]	1.45 [-0.31]	1.42 [-0.28]	1.36 [-0.64]	1.42 [-0.42]	1.42 [-0.31]
	Max	3.64 [0.40]	3.71 [0.41]	3.69 [0.18]	3.71 [0.24]	3.71 [0.19]	3.74 [0.13]	3.67 [0.24]

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 14 of 96)

CVT-301-008

Study Population: Safety

Parameter: Forced Expiratory Volume in 1 Second (L)

Treatment	Statistic	Timepoint						
		5 h	8 h	8.25 h	8.5 h	9 h	12 h	24 h
Placebo	n	25 [25]	25 [25]	25 [23]	25 [25]	24 [24]	25 [25]	25
	Mean	2.393 [0.023]	2.326 [-0.001]	2.323 [0.010]	2.336 [-0.028]	2.368 [-0.010]	2.286 [-0.008]	2.363
	SD	0.5961 [0.1954]	0.6527 [0.1332]	0.6771 [0.1576]	0.6583 [0.1917]	0.6364 [0.1062]	0.6144 [0.1358]	0.5575
	SE	0.1192 [0.0391]	0.1305 [0.0266]	0.1354 [0.0329]	0.1317 [0.0383]	0.1299 [0.0217]	0.1229 [0.0272]	0.1115
	Median	2.360 [0.030]	2.350 [0.010]	2.290 [0.020]	2.360 [-0.020]	2.370 [-0.015]	2.310 [0.030]	2.270
	Min	1.48 [-0.29]	1.22 [-0.47]	1.25 [-0.30]	1.09 [-0.56]	1.30 [-0.26]	1.36 [-0.22]	1.59
	Max	3.75 [0.58]	3.73 [0.17]	3.80 [0.26]	3.69 [0.21]	3.76 [0.24]	3.78 [0.34]	3.67

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 15 of 96)

CVT-301-008

Study Population: Safety

Parameter: Forced Expiratory Volume in 1 Second (L)

Treatment	Statistic	Timepoint						
		Predose	15 min	30 min	1 h	4 h	4.25 h	4.5 h
CVT-301	n	25 [24]	24 [24]	23 [21]	25 [25]	25 [25]	24 [22]	25 [24]
	Mean	2.366 [0.040]	2.216 [-0.169]	2.201 [-0.141]	2.276 [-0.119]	2.331 [-0.076]	2.238 [-0.182]	2.312 [-0.097]
	SD	0.5722 [0.1579]	0.6847 [0.2491]	0.7659 [0.2266]	0.7207 [0.2209]	0.6047 [0.2031]	0.7175 [0.2439]	0.6780 [0.2356]
	SE	0.1144 [0.0322]	0.1398 [0.0509]	0.1597 [0.0495]	0.1441 [0.0442]	0.1209 [0.0406]	0.1465 [0.0520]	0.1356 [0.0481]
	Median	2.290 [0.000]	2.225 [-0.105]	2.260 [-0.080]	2.290 [-0.080]	2.250 [-0.030]	2.220 [-0.070]	2.320 [-0.050]
	Min	1.51 [-0.23]	0.89 [-0.86]	0.87 [-0.76]	0.97 [-0.73]	1.35 [-0.49]	0.86 [-0.79]	0.88 [-0.64]
	Max	3.59 [0.38]	3.62 [0.12]	3.74 [0.16]	3.74 [0.17]	3.77 [0.20]	3.71 [0.16]	3.73 [0.49]

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 16 of 96)

CVT-301-008

Study Population: Safety

Parameter: Forced Expiratory Volume in 1 Second (L)

Treatment	Statistic	Timepoint						
		5 h	8 h	8.25 h	8.5 h	9 h	12 h	24 h
CVT-301	n	25 [25]	25 [25]	25 [23]	25 [25]	25 [25]	25 [25]	25
	Mean	2.326 [-0.044]	2.302 [-0.026]	2.190 [-0.137]	2.193 [-0.170]	2.290 [-0.064]	2.248 [-0.046]	2.336
	SD	0.6955 [0.2528]	0.6846 [0.2042]	0.7513 [0.2703]	0.7441 [0.2696]	0.7286 [0.1971]	0.6810 [0.2303]	0.6475
	SE	0.1391 [0.0506]	0.1369 [0.0408]	0.1503 [0.0564]	0.1488 [0.0539]	0.1457 [0.0394]	0.1362 [0.0461]	0.1295
	Median	2.260 [-0.060]	2.330 [0.030]	2.250 [-0.070]	2.240 [-0.120]	2.300 [-0.040]	2.260 [-0.030]	2.210
	Min	1.10 [-0.52]	0.87 [-0.64]	0.79 [-0.75]	0.76 [-0.84]	0.82 [-0.64]	0.95 [-0.65]	1.21
	Max	3.88 [0.71]	3.57 [0.37]	3.64 [0.17]	3.80 [0.25]	3.73 [0.26]	3.71 [0.34]	3.64

Source: Study CVT-301-008 CSR Table 14.3.5.3-1 pg 334-337

Mean Changes in Percent Predicted FEV1(L)

The same data as described above is presented in Table 14 as percent predicted FEV1. The percent predicted FEV1 did not change significantly in the placebo group. The mean percent predicted FEV1 in the CVT-301 treatment group never decreased more than 12% at any timepoint.

Table 14. Mean Changes in Percent Predicted FEV1 Averaged Over All Periods

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 29 of 96)

CVT-301-008

Study Population: Safety

Parameter: Percent Predicted FEV₁ (%)

Treatment	Statistic	Timepoint						
		Predose	15 min	30 min	1 h	4 h	4.25 h	4.5 h
Placebo	n	24 [23]	25 [25]	23 [21]	25 [25]	25 [25]	25 [23]	24 [23]
	Mean	79.5 [0.7]	79.2 [-0.3]	79.5 [-1.2]	79.9 [-0.6]	78.8 [-2.1]	79.4 [-2.4]	78.5 [-1.5]
	SD	11.84 [6.41]	11.95 [6.46]	12.54 [4.88]	13.49 [6.00]	12.99 [5.61]	12.07 [4.24]	11.37 [5.37]
	SE	2.42 [1.34]	2.39 [1.29]	2.61 [1.07]	2.70 [1.20]	2.60 [1.12]	2.41 [0.88]	2.32 [1.12]
	Median	79.0 [0.0]	79.0 [-1.0]	80.0 [-2.0]	80.0 [-1.0]	80.0 [-1.0]	81.0 [-2.0]	79.5 [-2.0]
	Min	57 [-8]	53 [-17]	56 [-12]	59 [-12]	56 [-14]	57 [-9]	53 [-10]
	Max	102 [18]	101 [17]	101 [7]	111 [10]	100 [8]	101 [5]	101 [10]

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 30 of 96)

CVT-301-008

Study Population: Safety

Parameter: Percent Predicted FEV₁ (%)

Treatment	Statistic	Timepoint						
		5 h	8 h	8.25 h	8.5 h	9 h	12 h	24 h
Placebo	n	25 [25]	25 [25]	25 [23]	25 [25]	24 [24]	25 [25]	25
	Mean	80.9 [0.8]	78.4 [-0.1]	78.1 [-0.1]	78.6 [-0.9]	79.0 [-0.2]	77.3 [-0.3]	80.1
	SD	11.50 [5.66]	13.17 [4.97]	14.17 [5.60]	13.59 [7.03]	13.36 [3.54]	11.93 [4.61]	10.42
	SE	2.30 [1.13]	2.63 [0.99]	2.83 [1.17]	2.72 [1.41]	2.73 [0.72]	2.39 [0.92]	2.08
	Median	82.0 [1.0]	81.0 [0.0]	80.0 [1.0]	79.0 [0.0]	81.5 [-0.5]	77.0 [1.0]	81.0
	Min	61 [-10]	45 [-18]	48 [-12]	42 [-21]	50 [-6]	52 [-10]	64
	Max	104 [12]	101 [6]	104 [8]	104 [8]	102 [8]	100 [8]	101

Table 14.3.5.3-1 Summary of Spirometry Data with Time-Matched Changes from Baseline

(Page 31 of 96)

CVT-301-008

Study Population: Safety

Parameter: Percent Predicted FEV₁ (%)

Treatment	Statistic	Timepoint						
		Predose	15 min	30 min	1 h	4 h	4.25 h	4.5 h
CVT-301	n	25 [24]	24 [24]	23 [21]	25 [25]	25 [25]	24 [22]	25 [24]
	Mean	80.0 [1.5]	73.9 [-6.0]	72.9 [-5.4]	76.4 [-4.3]	78.8 [-2.2]	75.2 [-6.2]	78.0 [-3.0]
	SD	9.52 [6.20]	16.01 [10.06]	18.08 [9.64]	16.33 [9.10]	11.87 [6.88]	16.91 [9.21]	16.12 [9.31]
	SE	1.90 [1.27]	3.27 [2.05]	3.77 [2.10]	3.27 [1.82]	2.37 [1.38]	3.45 [1.96]	3.22 [1.90]
	Median	79.0 [0.0]	78.0 [-3.0]	75.0 [-3.0]	81.0 [-3.0]	81.0 [-1.0]	76.0 [-2.5]	81.0 [-2.0]
	Min	65 [-9]	34 [-39]	33 [-34]	44 [-33]	52 [-15]	33 [-31]	34 [-25]
	Max	103 [15]	100 [5]	102 [7]	103 [7]	100 [8]	103 [5]	102 [23]

Study Population: Safety

Parameter: Percent Predicted FEV₁ (%)

Treatment	Statistic	Timepoint						
		5 h	8 h	8.25 h	8.5 h	9 h	12 h	24 h
CVT-301	n	25 [25]	25 [25]	25 [23]	25 [25]	25 [25]	25 [25]	25
	Mean	78.0 [-2.1]	77.3 [-1.2]	73.4 [-5.0]	73.4 [-6.1]	76.7 [-2.6]	75.5 [-2.1]	78.5
	SD	14.24 [8.36]	15.18 [8.11]	19.15 [10.65]	17.59 [10.34]	16.21 [7.95]	14.69 [8.94]	12.03
	SE	2.85 [1.67]	3.04 [1.62]	3.83 [2.22]	3.52 [2.07]	3.24 [1.59]	2.94 [1.79]	2.41
	Median	82.0 [-2.0]	78.0 [1.0]	79.0 [-2.0]	79.0 [-4.0]	79.0 [-1.0]	78.0 [-1.0]	79.0
	Min	50 [-24]	40 [-29]	31 [-33]	35 [-33]	37 [-30]	37 [-30]	55
	Max	103 [15]	105 [12]	101 [7]	101 [8]	105 [6]	102 [13]	100

IV. Previous DPARP Consults and Recommendations

- PIND meeting November 27, 2012: DPARP provided the following recommendations to the sponsor
 - For evaluation of acute bronchospasm, we recommend conducting safety studies in three different populations: healthy volunteers, asthmatics, and cigarette smokers. Since you anticipate dosing CVT-301 three times daily, consider evaluating a single day of three times daily dosing. We recommend spirometry starting at 15 minutes after the first dose and including frequent spirometric measurements for 24 hours after the final dose. We recommend asthmatics be included as a special population as they are the most sensitive patient population for bronchospasm. In the inhaled insulin program, smoking increased drug exposure; therefore, pharmacokinetics of smokers using CVT-301 need to be evaluated in addition to spirometry.
 - Although it is premature to discuss a phase 3 protocol at this point, some general comments are as follows:
 - DPARP recommends 12-month safety data. We agree with your proposal for a 12-month long-term pulmonary safety study. You should be sure to include patients who are representative of the patient population for which CVT-301 would be indicated, advanced PD patients who are likely older and may have concomitant medical illnesses.
- IND Opened February 4, 2013: DPARP provided these Non-Hold comments
 - The IND was opened with study CVT-301-003, a phase 2b, R, PC study in 86 subjects with PD, randomized 1:1:1 to 35 mg CVT-301, 50 mg CVT-301, or placebo. DPARP provided the following recommendations regarding pulmonary safety testing in Protocol CVT-301-003:
 - Perform post-dose spirometry testing at all visits during the treatment period, not just at Visit 3 and 5. Include measurements at 15, 30, and 60 minutes post-dose at all visits.
 - You propose that patients who have a decrease in forced expiratory volume in 1 second (FEV₁) $\geq$ 15% AND a decrease in FEV₁ by 200 mL AND a reduction in FEV₁/forced vital capacity (FVC) ratio to <70% compared with pre-dose (OFF) results, will not be sent home with study drug (post-inhalational bronchospasm). Remove the criteria for FEV₁/FVC ratio. The FEV₁/FVC ratio may be normal during severe respiratory compromise if both FEV₁ and FVC are reduced. In addition, interpretation of this ratio may be complicated by the patient's disease state and the activity of the drug.

- You propose employing spirometry-based stopping criteria for post-inhalational bronchospasm only for Visit 3 (first dose of study drug). Use similar stopping criteria for all clinic visits as post-inhalational bronchospasm may be worsened with recurrent dosing.
- Include evaluation of post-inhalational cough and recording of respiratory adverse events (AEs) at each study visit.
- Perform spirometry testing according to American Thoracic Society (ATS) Criteria. See Brusasco V, Crapo R, Viegi G, ed. Standardization of Spirometry. *Eur Respir J* 2005; 26:319-38

On 8/2/13, the sponsor provided the following acceptable rationale not to incorporate comments 1-3, as detailed below:

- Comment 1: The protocol states that spirometry will be assessed at Visit 3 (pre, post 15, 30, and 60 minutes) and Visit 5 (baseline, pre, and post 60 minutes). Spirometry assessment at visits other than Visit 3 (week 1: first inhaled dose) and Visit 5 (week 3: dose escalation from 35 to 50mg) interferes with critical efficacy evaluations. Furthermore, previous clinical studies show no adverse events on pulmonary function, as assessed by routine spirometry. A blinded-safety review will occur at 2 time points during the study: after 12 subjects complete Visit 3 and after 12 subjects complete all study treatment visits. Of note, spirometry is assessed pre-dose at Visit 4 (week 2) and Visit 6 (week 5: end-of- treatment).
- Comment 2: True expiratory airflow obstruction, as defined by a reduced FEV1/FVC ratio, is not common in Parkinson's patients. This is most likely due to chest wall dysfunction with problems with muscular tone or coordination, which lower FEV1 and similarly FVC. Including the FEV1/FVC ratio in the stopping criteria will help to identify patients with true acute obstruction.
- Comment 3: Post-inhalation bronchospasm has not been seen in previous clinical studies. The sponsor states that numerous safe guards are provided and the first-dose and increases in dosage are performed under direct medical supervision.
- EOP2 meeting package opened May 2, 2014: DPARP consulted to comment on pulmonary safety submitted with the EOP2 meeting package for CVT-301. Recommendation was made for Civitas to collect devices (both those that were noted to be working properly (at least 100 with active treatment and those that were identified as having problems) for in vitro testing at the end of the phase 3 study. Include a control group within the long term 12 month safety studies Study 004E and 005 to provide for comparison between inhaled and non-inhaled groups within the same study.
- Pre-NDA opened September 1, 2016:
 - DPARP commented on the use of pulmonary function test (PFT) laboratory spirometry data in the primary analysis of pulmonary safety. There were two sources of PFT data the neurology centers and the PFT laboratories and there was a difference between the collection of data at the two sites. While it was thought to be acceptable to use the PFT lab spirometry data in the primary analysis it was recommended that a sensitivity analysis of the data from the neurology study sites be conducted to ensure these differences had no impact on the pulmonary safety profile of CVT-301.

Reviewer's comment;

The sponsor did Study-007 an OL, PG, SD study in 56 HV smokers and non-smokers to evaluate the PK, safety and pulmonary safety of CVT-301. Following inhaled doses of CVT-301 84mg the median maximal plasma concentration (tmax) of levodopa was achieved at 30 minutes in non-smokers and at 45minutes in smokers. The mean maximal plasma concentration (Cmax) of levodopa after inhalation of CVT-301 was slightly higher (765ng/ml) in smokers than non-smokers (684 ng/ml). Cough was the most common TEAE and occurred 71% in non-smokers and 60% in smokers. Smoking has previously been shown to increase systemic exposure of inhaled compounds and although point estimates for AUC₀₋₂₄ and Cmax for levodopa were higher in smokers this may not be clinically significant.

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/s/

MARY T O'DONNELL
08/15/2018

BANU A KARIMI SHAH
08/15/2018