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A 12-month, dose-level blinded safety and efficacy study of levodopa inhalation powder (CVT-301, Inbrija) in patients with Parkinson's disease

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ABSTRACT

Introduction: CVT-301 (Inbrija®) is a levodopa inhalation powder for on-demand treatment of OFF episodes in Parkinson's disease patients treated with carbidopa/levodopa. Safety and efficacy results of a 12-month, dose-level blinded extension study of a phase 3 trial (SPAN^{SM}-PD) of CVT-301 are presented.

Methods: Patients were receiving oral carbidopa/levodopa and adjunctive CVT-301 treatment, blinded to dose (60 mg or 84 mg, N = 325). Study visits occurred every 3 months. Pulmonary function was assessed by spirometry. Other safety assessments included dyskinesia and adverse events (AEs). Secondary objectives of the study included maintenance of improvement assessments for occurrence of an ON state during the 60-min post-dose period, change in total daily OFF time, and Patient Global Impression of Change (PGIC).

Results: Most frequent AEs (≥5%) were cough (15.4%), fall (13.1%), upper respiratory tract infection (7.1%), and dyskinesia (5.1%). Severe AEs (>1 event) were cough (1.9%) and dyskinesia (0.6%). Twelve-month mean changes from baseline for FEV_1, FVC, and DL_{CO} were −0.092 L, −0.097 L, and −0.922 mL/min/mmHg, respectively. At 12 months, 73.0% of patients on 84 mg achieved an ON state within 60 min. Total daily OFF time was reduced by 0.55 h (month 1) and 0.88 h (month 12) for the 84 mg dose. Percentage of patients self-reported as improved by PGIC was 65.5–91.9% over 12 months.

Conclusion: CVT-301 was generally well-tolerated. Twelve-month decline in pulmonary function was consistent with a prior PD control group. Exploratory efficacy results showed CVT-301 maintained improvement at achieving ON states in patients experiencing OFF episodes, decreasing daily OFF time, and maintaining improvement in PGIC.

1. Introduction

Though highly effective for treating the motor features of Parkinson's disease (PD) [1], levodopa has a relatively short plasma clearance half-life (approximately 90 min when co-administered with carbidopa [CD] [2]). Almost half of patients experience OFF episodes by 4–6 years after starting treatment, and by 10 years, almost all patients [3]. Use of oral LD to treat OFF periods is problematic over time because of its increasingly variable gastrointestinal absorption. Until recently, subcutaneous apomorphine injection was the only indicated treatment for on-demand relief of OFF episodes.

CVT-301 (Inbrija®) is an orally inhaled LD powder approved for the treatment of OFF episodes in patients with PD treated with carbidopa/levodopa (CD/LD). Pulmonary delivery of LD with CVT-301 avoids problems of absorption in the gastrointestinal tract. Clinical trials with CVT-301 showed that it provided reliable and uniform delivery of LD to the systemic circulation [4]. In a 12-week, phase 3 trial (SPAN-PD) involving 351 patients experiencing motor fluctuations, CVT-301 significantly improved Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (motor) scores [5] versus placebo at 30 min after dosing [6]. The onset of improved UPDRS-III scores was evident at 10 min. Treatment with CVT-301 was generally safe and well-tolerated. There

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was also a statistically significant difference in the proportion of patients who, at the 12-week assessment, maintained an ON response through 60 min: 56 of 97 (58%) in the CVT-301 84 mg group versus 35 of 97 (36%) in the placebo group [6]. Furthermore, a previous 12-month, open-label, randomized, controlled study showed that patients on adjunctive CVT-301 were not associated with clinically significant difference in pulmonary function compared with an observational cohort receiving conventional oral CD/LD regimens [7].

The study described here was a 52-week extension study of the phase 3 SPAN℠-PD study designed primarily to evaluate the safety of two dose levels of CVT-301 as adjunct to daily oral CD/LD in patients with PD and OFF episodes.

2. Methods

A 12-month, dose-level blinded, multicenter study (ClinicalTrials.gov NCT02242487) was conducted in North America and Europe to evaluate pulmonary safety of two inhaled dose levels of CVT-301 in patients with PD experiencing motor fluctuations. CVT-301 (60 mg or 84 mg) was self-administered by patients as needed, up to 5 times per day. Study design is shown in Fig. 1A.

2.1. Ethics statement

The protocol, a patient information sheet, informed consent form, and other relevant study documentation were approved by ethics committees or institutional review boards of each site before study initiation. The study was conducted in accordance with ethical principles originating from the Declaration of Helsinki and consistent with good clinical practice and applicable regulatory requirements. Before enrollment, all patients provided written informed consent.

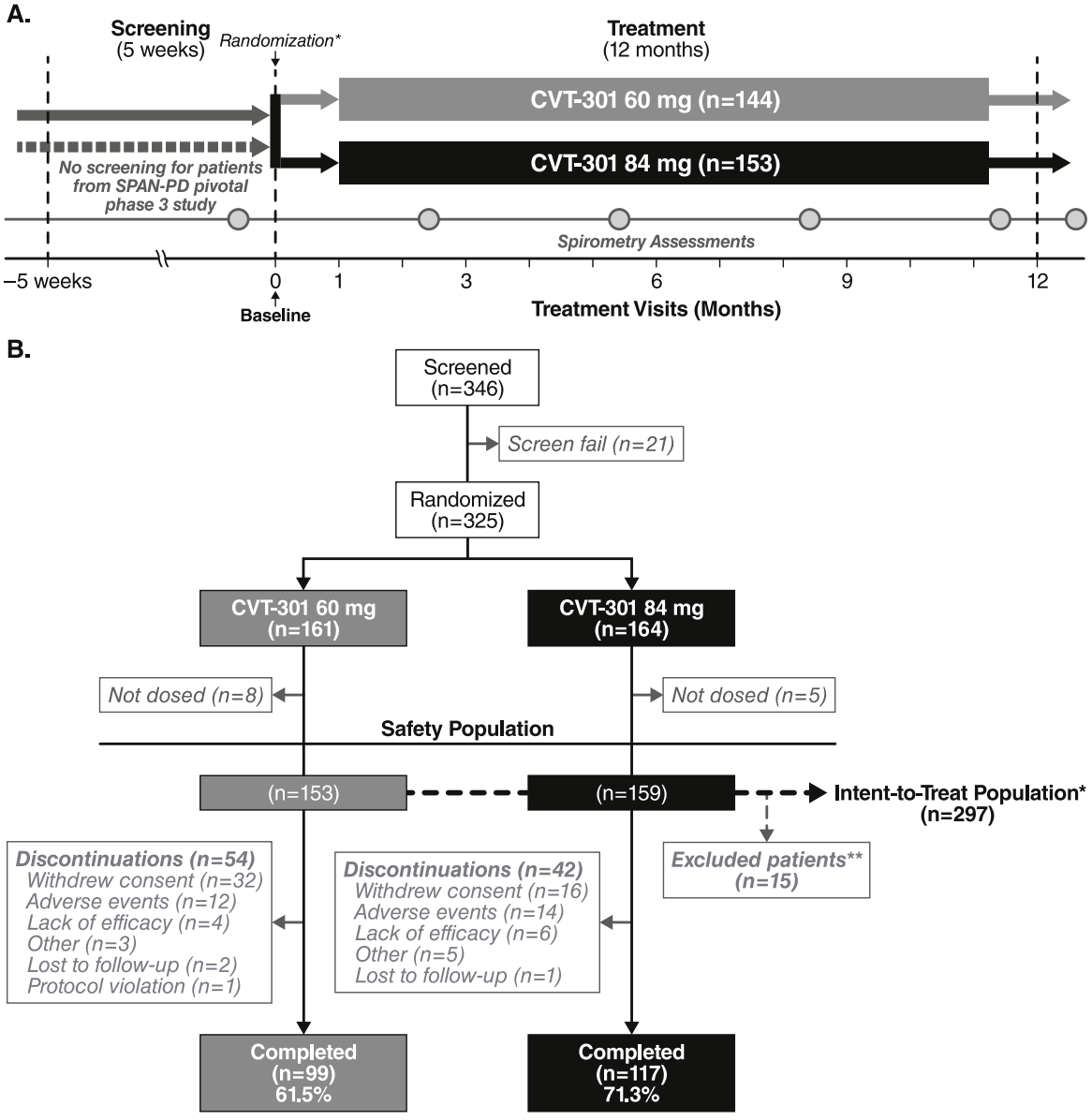

Fig. 1. Study design (A) and patient disposition (B).
*Intent-to-treat population was composed of 60 mg (n = 144) and 84 mg (n = 153) dose groups.
**Intent-to-treat population excluded patients from other studies apart from SPAN-PD because of small population numbers, different study designs, and time gaps to the start of the study.

2.2. Subjects

This extension study included patients from previous CVT-301 trials and treatment-naïve patients. Inclusion criteria included: diagnosis of idiopathic PD (UK Brain Bank Criteria [8]); Hoehn and Yahr stages 1–3 [9] assessed when the patient was in an ON state; aged between 30 and 86 years; and experiencing motor fluctuations with a minimum average of 2 h OFF time per waking day.

2.3. Randomization and blinding

Patients from the CVT-301 treatment group of the SPAN-PD study had a 1- to 14-day period between the last dose of CVT-301 in SPAN-PD and the first dose of study drug in this study and were maintained on the same dose level. Placebo-treated patients from the SPAN-PD trial and patients who had not participated in SPAN-PD were randomized in a 1:1 blinded fashion to receive either 60 mg or 84 mg CVT-301. Randomization was stratified by 1) Hoehn and Yahr scale rating (<2.5 vs ≥ 2.5) during the ON state to balance for disease severity across dose groups, and 2) screening spirometry using FEV_1 (forced expiratory volume in 1 s) and FVC (forced vital capacity) (FEV_1 $<60\%$ of predicted or FEV_1/FVC ratio <0.7 vs FEV_1 $\geq 60\%$ of predicted and FEV_1/FVC ratio of ≥ 0.7). The dose level for all patients remained double-blinded for the entire study. To maintain blinding, CVT-301 capsules and packaging for each dose were identical in appearance.

2.4. Treatment and study visits

All patients continued with their usual prescribed standard oral PD medication regimen for the screening period of up to 35 days and treatment period of approximately 12 months. Patients were trained on inhaler use with sham capsules during the screening period and self-administered CVT-301 when they experienced OFF periods during clinic visits and at home. The study drug could be used up to 5 times daily at home. Initially, the drug could not be used for treatment of early morning OFF periods (ie, for morning akinesia before the first ON period of the day). However, after data from another study [10] became available supporting the safety and tolerability of CVT-301 administration in the early morning, participants were permitted to take CVT-301 with their first morning CD/LD dose for treating initial OFF periods during the remainder of the study. Patients were instructed not to take CVT-301 within 45 min after a previous dose of standard oral PD medication. Each treatment consisted of two capsule inhalations (two 30 mg or 42 mg LD capsules); however, if not tolerated, dose reduction was permitted. Patients completed daily logs to record inhaler use. Planned visits occurred at day 1 and at approximately 1, 3, 6, 9, and 12 months when safety evaluations and maintenance of improvement assessments were performed. Acute spirometry measures were collected during the planned visits, while chronic pulmonary function tests and carbon monoxide diffusing capacity (DL_{CO}) measures were assessed in patients during an ON state at pulmonary function laboratories within two weeks prior to each visit. Safety data were reviewed by an independent data safety monitoring board.

2.5. Outcome measures

The primary objective of the study was to characterize the effects of CVT-301 on pulmonary safety as assessed by spirometry over a 12-month period. Pulmonary measurements were FEV_1, FVC, FEV_1/FVC ratio, and DL_{CO}, for which a negative change may indicate decline in pulmonary function. FEV_1, a measure of airway obstruction [11], declines about 30–40 mL annually in nonsmoking Caucasian individuals and is age-dependent [12]. FVC is the total volume of air forcibly expired after maximal inspiration. FEV_1 and FVC, together with the FEV_1/FVC ratio, can be used to differentiate restrictive and obstructive lung diseases. In healthy subjects, FEV_1/FVC is approximately 0.8 (80%); a lower FEV_1/FVC ratio, in addition to decreased FEV_1 and decreased or normal FVC, is characteristic of obstructive lung disease. A normal FEV_1/FVC ratio, normal or decreased FEV_1, but decreased FVC, indicates restrictive lung disease. DL_{CO} is a measure of gas exchange between lungs and bloodstream [13].

Maintenance of improvement assessments included: 1) proportion of patients achieving resolution of an OFF state to an ON state within 60 min after CVT-301 administration in the clinic and maintaining the ON state at 60 min (as assessed by study personnel during the treatment visits), and 2) proportion of patients who self-reported improvement on the Patient Global Impression of Change (PGIC) rating scale. Assessments from patient-reported PD diaries [14] included 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. Other secondary improvement outcomes were change from baseline in the 39-item Parkinson's Disease Questionnaire (PDQ-39) [15], Schwab and England (S&E) Activities of Daily Living score [16]; 9-item Patient Health Questionnaire (PHQ-9); Impact of Parkinson's Off Episode Patient Survey score; and the UPDRS [17] Part II (activities of daily living) score. Secondary safety assessments included AE reports, physical examination, standard and orthostatic vital signs (blood pressure, heart rate, and respiratory rate), clinical laboratory tests, 12-lead electrocardiograms, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease [18], Epworth Sleepiness Scale [19], and Columbia-Suicide Severity Rating Scale [20]. Reported AEs were volunteered spontaneously by the patient, discovered as a result of general questioning by the study staff, or determined by physical examination. At each visit, the patient was asked, "Have you experienced any problems since your last visit?" Each AE was also described in terms of duration, frequency, intensity, association with the study drug, assessment of possible causes, actions taken, and outcome. All AEs were recorded in standard medical terminology (MedDRA version 19.1).

2.6. Statistical analysis

Statistical analyses evaluated pulmonary function as well as efficacy. Changes from baseline in FEV_1, FVC, FEV_1/FVC, and DL_{CO} were summarized descriptively and categorically in increments of 10% from increases of $>50\%$ to decreases of -50% based on the safety population. Changes in spirometry values within each dose group and differences between dose groups were estimated with a mixed model for repeated measurements (MMRM) model. For the efficacy analysis, the intent-to-treat population was used. Efficacy variables were summarized descriptively. Changes from baseline in continuous efficacy variables were estimated using a similar MMRM model. Baseline values for efficacy analysis were defined as the last efficacy assessment before the first exposure to CVT-301. For patients who carried over from the SPAN-PD CVT-301 groups, baseline values were taken from the start of SPAN-PD. For patients from the SPAN-PD placebo group or other CVT-301-naïve patients, the baseline was from the start of this study.

Subgroup analyses were performed on change in OFF time by gender, age (<65 years at baseline versus ≥ 65 years), PD severity (baseline severity on Hoehn and Yahr scale <2.5 versus ≥ 2.5 points), daily LD dose (baseline daily LD dose $\leq$ median versus $>$ median dose), mean daily OFF time (PD diary mean daily OFF time at baseline <4.5 versus ≥ 4.5 h), dyskinesia (baseline ≥ 1 h dyskinesia [ON with troublesome or non-troublesome dyskinesia] over previous 2 days versus no recorded dyskinesia), and pulmonary function (baseline FEV_1 60% of predicted or FEV_1/FVC ratio <0.7 versus FEV_1 $\geq 60\%$ of predicted and FEV_1/FVC ratio ≥ 0.7). Statistical software was SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Study population

Of 325 patients randomized, 237 (72.9%) were from the phase 3 SPAN-PD trial (154, CVT-301 arm; 83, placebo arm), 45 (13.8%) from other CVT-301 trials, and 43 (13.2%) who were not previously enrolled in a CVT-301 study. A total of 216 (66.5%) patients completed the study and 109 (33.5%) did not complete (Fig. 1 B). The intent-to-treat population (n = 297) excluded 15 patients from other studies (apart from SPAN-PD) because of small population numbers, different study designs, and time gaps to the start of the study. Patient demographics, baseline spirometry, and PD severity were similar between the two treatment groups (Table 1).

Mean number of CVT-301 doses was 1.9 per day (mean range 1.0–4.8 per day), and mean duration of exposure was 292.9 days (SD 131.8). Mean number of doses per day in the first month was 1.9 (mean range 1.0–5.0) for 60 mg and 2.0 (mean range 1.0–4.8) for 84 mg, and for months 9–12, 2.0 (mean range 1.0–4.8) for 60 mg and 2.0 (mean range 1.0–4.9) for 84 mg. Overall, 24.4% of patients used 5 doses/day at least once, 55.8% used at least 4 doses/day at least once, and 78.5% used 3 doses/day at least once.

Table 1
Baseline demographic, spirometry, and PD characteristics.

Characteristic	CVT-301		
	60 mg (n = 153)	84 mg (n = 159)	Total (n = 312)
Mean age, years	63.9	62.9	63.4
Gender, n (%)			
Male	110 (71.9)	119 (74.8)	229 (73.4)
Female	43 (28.1)	40 (25.2)	83 (26.6)
Ethnicity, n (%)			
Hispanic or Latino	4 (2.6)	5 (3.1)	9 (2.9)
Not Hispanic or Latino	149 (97.4)	154 (96.9)	303 (97.1)
Race, n (%)			
White	147 (96.1)	150 (94.3)	297 (95.2)
Black or African American	3 (2.0)	3 (1.9)	6 (1.9)
Asian	1 (0.7)	5 (3.1)	6 (1.9)
American Indian/Alaska native	0	1 (0.6)	1 (0.3)
Native Hawaiian/Pacific Islander	1 (0.7)	0	1 (0.3)
Other	1 (0.7)	0	1 (0.3)
Mean BMI (kg/m^2)	27.7	27.6	27.6
PD severity, Hoehn and Yahr stage, n (%)			
<2.5 points	94 (61.4)	97 (61.0)	191 (61.2)
≥2.5 points	59 (38.6)	62 (39.0)	121 (38.8)
Screening spirometry			
FEV_1 <60% and FEV_1/FVC <0.7, n (%)	8 (5.2)	10 (6.3)	18 (5.8)
FEV_1 ≥60% and FEV_1/FVC ≥0.7, n (%)	145 (94.8)	149 (93.7)	294 (94.2)
Mean time from diagnosis of PD, months (SD)	103.4 (55.4)	99.3 (47.8)	101.3 (51.6)
Mean duration of LD treatment, months (SD)	86.7 (56.4)	83.7 (46.9)	85.2 (51.7)
Mean daily LD dose, mg (SD)	870.1 (372.7)	895.3 (412.5)	883.0 (393.1)
Mean daily LD doses, n (SD)	5.1 (1.6)	5.1 (1.5)	5.1 (1.5)
Screening PD diary			
Mean number of daily OFF episodes, hrs (includes AM) (SD)	3.46 (1.02)	3.56 (1.10)	3.51 (1.06)
<4.5 h daily OFF time during screening, n (%)	59 (38.6)	57 (35.8)	116 (37.2)
≥4.5 h daily OFF time during screening, n (%)	94 (61.4)	102 (64.2)	196 (62.8)
Mean daily OFF time, hrs (includes AM) (SD)	5.35 (2.11)	5.23 (2.13)	5.29 (2.12)
Mean daily ON time without dyskinesia, hrs (SD)	8.59 (3.42)	8.47 (3.49)	8.53 (3.45)

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, forced expiratory volume in 1 s divided by forced vital capacity; hrs, hours; LD, levodopa; PD, Parkinson's disease.

3.2. Pulmonary safety

Overall, 12-month mean changes from baseline were −0.092 L for FEV_1, –0.097 L for FVC, 0.4% for FEV_1/FVC, and −0.922 mL/min/mmHg for DL_{CO}. There were no apparent meaningful differences between dose groups at any timepoint for mean change from baseline in FEV_1, FVC, or FEV_1/FVC ratio (Fig. 2). For DL_{CO}, most patients experienced change between −10% and <10% over the course of the study (range, 79.8% of patients at week 12–69.4% at week 52). The DL_{CO} changes for the two dose groups were similar.

3.3. Adverse events

CVT-301 at the two study doses was generally safe and well-tolerated; 218 (69.9%) patients experienced at least one treatment-emergent adverse event (TEAE). Overall, 35 patients (11.2%) experienced a serious adverse event (SAE), 22 (14.4%) in the 60 mg group and 13 (8.2%) in the 84 mg group. The most common AEs (>3%) are shown in Table 2. One patient in the 84 mg group experienced an SAE of impulse control disorder, which was assessed by the investigator as being possibly related to study drug; this event was reported as resolved. All other SAEs were assessed as definitely not related, or unlikely related to treatment.

Fifty-five instances of treatment-emergent cough were reported by 48 patients. Slightly more than half (25/48) reported cough starting within the first 30 days of treatment. Of the 55 instances, 34 (62%) were mild, 15 (27%) moderate, and 6 (11%) severe. Forty-one TEAEs (88%) of cough in 36 patients were assessed as being related to study drug. All but one patient recovered or were recovering at the end of the study; one patient was lost to follow-up. No TEAE of cough was assessed as serious. Two TEAEs of cough led to reduction of dose (from 84 to 60 mg), and 7 to study withdrawal (4 patients, 60 mg; 3 patients, 84 mg). Two TEAEs of productive cough were reported in the 60 mg dose group, both classified as drug-related, with one considered mild and one moderate.

The severe drug related TEAEs were cough (6 patients), dyskinesia (2 patients), hallucinations, anxiety, delusion, laryngitis (1 patient each), and muscle spasms and sleep disorder (1 patient each in the 60 mg dose group). The severe events of anxiety and dyskinesia occurred in 1 patient, and the severe events of dyskinesia, delusion, and hallucinations also occurred in 1 patient.

The occurrence of dyskinesia during the 60-min post-dose period was examined at each treatment visit and the examiner recorded the maximum severity of any dyskinesia. The overall incidence of examiner-rated dyskinesia after dosing showed no clear trend over time, ranging from 35 patients (11.2%) to 53 patients (17.0%) overall during the 60-min post-dose interval over 6 treatment visits. Most occurrences were mild or moderate in severity, and no severe dyskinesia was reported. The 60 mg dose group had lower observed dyskinesia than the 84 mg group, with the greatest difference in incidence of patients with observed dyskinesia at 1 month (12.4% in 60 mg group; 21.4% in 84 mg group).

3.4. Maintenance of improvement assessment

A secondary objective of this study was improvement assessment. Successful ON state was defined as patients who achieved resolution of their OFF state within 60 min after study drug administration and maintained this ON state at 60 min as assessed by study personnel during the in clinic assessments. By examiner subjective assessment, between 67.7 and 83.6% of all patients achieved a successful resolution of their OFF state to an ON state within 60 min of CVT-301 use at either dose and across all treatment visits (Suppl Fig. 1A).

The percentage of patients who reported themselves "improved" (ie, "a little improved," "improved," or "much improved") on PGIC ranged from 65.5 to 91.9% across all treatment visits; these values were higher in the 84 mg group at every timepoint (Suppl Fig. 1B). In general, the percentage of patients who rated themselves as improved increased

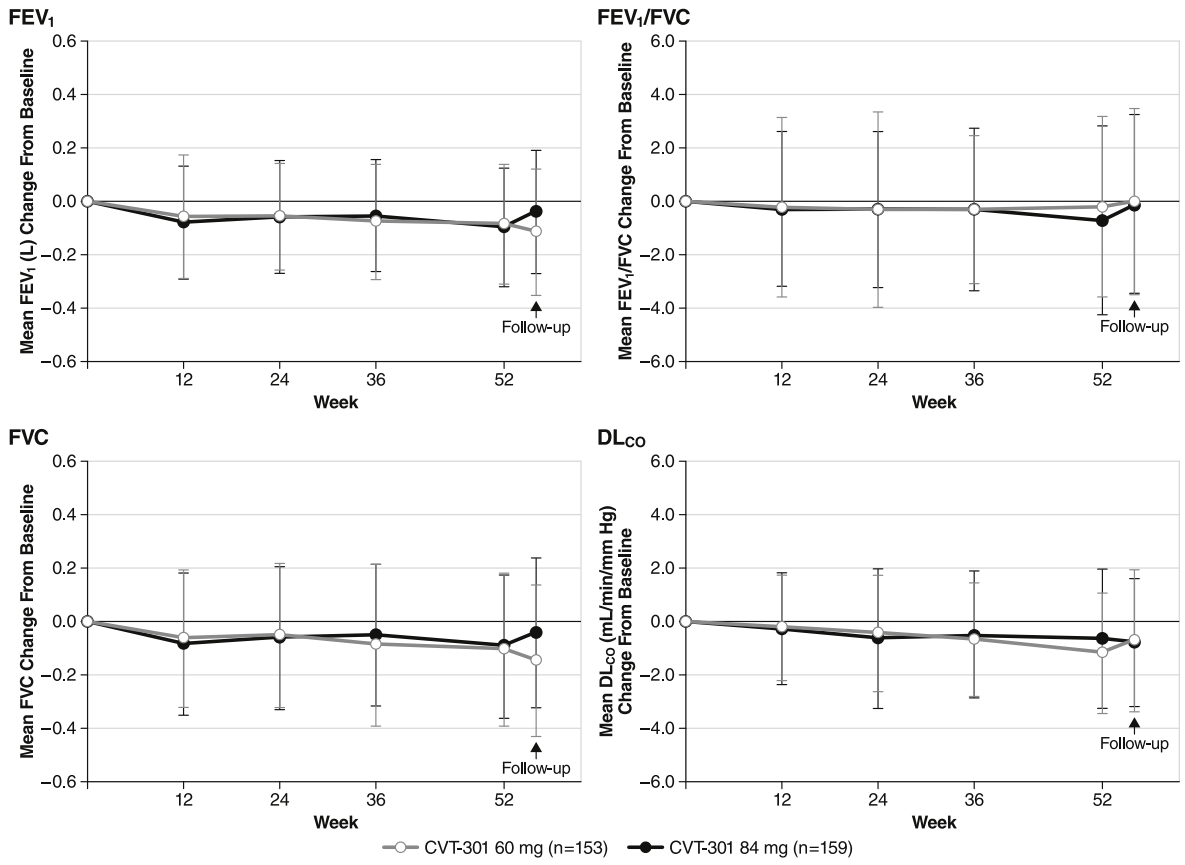

Fig. 2. Pulmonary function changes over 52 weeks.
Error bars show standard deviation.
DL_{CO}; carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2
Adverse events.

	CVT-301		
	60 mg (n = 153)	84 mg (n = 159)	Total (n = 312)
Any TEAE	103 (67.3)	115 (72.3)	218 (69.9)
Serious TEAEs	22 (14.4)	13 (8.2)	35 (11.2)
TEAEs leading to death	0	0	0
TEAEs leading to withdrawal	12 (7.8)	14 (8.8)	26 (8.3)
Drug-related TEAEs[a]	45 (29.4)	51 (32.1)	96 (30.8)
Severe TEAEs	19 (12.4)	12 (7.5)	31 (9.9)
TEAEs ≥ 3% of patients in any treatment group			
Cough	25 (16.3)	23 (14.5)	48 (15.4)
Fall	24 (15.7)	17 (10.7)	41 (13.1)
Upper respiratory tract infection	10 (6.5)	12 (7.5)	22 (7.1)
Dyskinesia	6 (3.9)	10 (6.3)	16 (5.1)
Throat irritation	7 (4.6)	5 (3.1)	12 (3.8)
Nasopharyngitis	8 (5.2)	4 (2.5)	12 (3.8)
Back pain	8 (5.2)	3 (1.9)	11 (3.5)
Constipation	5 (3.3)	7 (4.4)	12 (3.8)
Pain in extremity	6 (3.9)	2 (1.3)	8 (2.6)
Arthralgia	5 (3.3)	4 (2.5)	9 (2.9)
Dizziness	5 (3.3)	4 (2.5)	9 (2.9)
Urinary tract infection	5 (3.3)	4 (2.5)	9 (2.9)
Contusion	5 (3.3)	1 (0.6)	6 (1.9)
Parkinson's disease	5 (3.3)	0	5 (1.6)
Basal cell carcinoma	0	5 (3.1)	5 (1.6)

[a] AEs were considered drug-related if the event was classified as possibly, probably, or definitely related to study drug by investigators. TEAE, treatment-emergent adverse event.

through week 24, after which it decreased in both groups. As the end-of-study visit was assigned to week 52 for patients who withdrew early, lower improved responses at week 52 may be attributable to early withdrawals. Suppl Fig. 1B shows post hoc data that exclude the early withdrawals for week 52.

Patients' OFF times were recorded in PD diaries for 3 consecutive days before visits at weeks 4 through 52. Over time, the magnitude of change from baseline increased for both doses (Suppl Fig. 2). Least squares mean reduction in OFF time (95% CI) at week 52 from baseline was −0.88 h (−1.34, −0.43) for 84 mg and −0.7 h (−1.17, −0.23) for 60 mg. Results of the subgroup analysis of change from baseline in total daily OFF time for baseline PD severity, dyskinesia, daily LD dose, age, and screening spirometry showed no clear differences in the sub-analyses. However, patients who had <4.5 h of daily OFF time during the screening had a smaller response when compared with those who had ≥4.5 h (change with 84 mg dose and <4.5 h OFF at screening was −0.38 h [–1.01, 0.26]; for ≥4.5 h it was −1.11 h [–1.74, −0.47]). Also, female patients showed less change from baseline OFF time than male patients. For the 84 mg dose, the least squares mean difference from screening at week 52 was −0.71 h (−1.62, 0.20) for females and −0.84 h (−1.38, −0.30) for males. Change from baseline in daily ON time without dyskinesia improved from +0.23 to + 0.18 h at month 1 to +0.32 and + 0.40 h at week 52 for 60 mg and 84 mg, respectively.

No consistent trends were observed in change from baseline for total daily ON time (ON time with or without troublesome dyskinesia), UPDRS Part II, S&E score, PDQ-39 score, PHQ-9 score, or the Impact of Parkinson's OFF Episode Patient Survey over the 52-week period. Further details are shown in Suppl Table 1 and in the Suppl Secondary Improvement Results Summary.

4. Discussion

In this one-year extension study to evaluate pulmonary safety, CVT-301 was safe and generally well-tolerated. Changes in pulmonary function by spirometry and DL_{CO} were similar to those in a previous long-term pulmonary study that found no statistically significant differences over one year between CVT-301 and observational controls [7]. There was a slight decline in pulmonary function, with most patients experiencing <10% change from baseline in both spirometry and DL_{CO} parameters. No notable difference in chronic pulmonary assessments differentiated the 60 mg and 84 mg doses. On clinic pulmonary evaluations, most patients had <10% change from pre-dose values and tolerated exposure well. TEAEs were generally consistent with those for oral LD except for cough, an expected side-effect with dry powder inhalation, previously reported with CVT-301 [6,10]. Most cough AEs were mild, and all resolved by end of study (although one patient was lost to follow-up). Overall, AEs were consistent with the previous phase 3 study, and both 60 mg and 84 mg were safe and well-tolerated. There were no adverse safety signals derived from review of vital signs, physical exams, clinical laboratory values, or electrocardiograms. Secondary efficacy endpoints suggested that improvement was maintained throughout the study. The proportion of patients converting from OFF to ON within 60 min and maintenance of ON at 60 min was supported by PGIC and patient diaries, suggesting continued improvement over 52 weeks and greater improvement in the 84 mg treatment group.

In a previous 12-month, open-label, randomized, controlled study by Grosset et al. patients on adjunctive CVT-301 84 mg also had slight decline in pulmonary function with no clinically significant difference compared with an observational cohort receiving immediate-release oral LD [7]. Mean change from baseline at 12 months for the observational cohort and CVT-301, respectively, was −0.117 L and −0.105 L for FEV_1, –0.125 L and −0.155 L for FVC, and −0.722 mL/min/mmHg and −0.378 mL/min/mmHg for DL_{CO} [7]. Overall pulmonary function changes observed in this study (−0.092 L for FEV_1, –0.097 L for FVC, and −0.922 mL/min/mmHg for DL_{CO}) were similar. For patients with chronic obstructive pulmonary disease (COPD), a commonly-accepted minimal clinically important difference (MCID) for FEV_1 is 0.1 L [21]; in this study the 52-week treatment change was −0.092 L. For FEV_1/FVC, an MCID has not been established. The MCID for DL_{CO} in patients with COPD is 1.1 mL/min/mmHg [22]; the treatment difference here was −0.922. This suggests that decline in pulmonary function approached clinical significance. However, the earlier study [7] showed a similar decline in FEV_1 and DL_{CO} in the observational group, suggesting that pulmonary decline is related to PD progression rather than CVT-301 inhalation [23]. The mean number of doses taken per day during the present study was about 2. Baseline PD characteristics showed a mean number of 3.51 OFF periods per day, which includes the early morning OFF period. Patients were instructed to avoid using CVT-301 for their early morning OFF period prior to their oral CD/LD dose because CD levels in the morning would be low. This was investigated in another study [10] which assessed the safety of CVT-301 when given for morning OFF, after which patients were permitted to take it for early morning OFF. Therefore, for much of the time, the mean number of daily OFF periods that patients were allowed to treat with CVT-301 in the study (which excluded morning OFF) was approximately 2.5 OFF periods daily. Further, there may be situations in which patients may elect not to treat their OFF periods, such as in the evening before sleeping. In conclusion, the average dose frequency of 2 doses a day reflects the real need of supplemental LD during the active period of the day. This takes into account that CVT-301 administration was restricted for the early morning OFF period and that there is no need for it shortly before the patient's bedtime. A conservative interpretation, however, would conclude that average dosing of up to twice per day appears to show no significant change in pulmonary function over 12 months, but long-term safety has not yet been demonstrated at maximally recommended dosages. Continued post marketing surveillance is appropriate.

An important limitation of this study is that there was no placebo arm, so there was no control population for both the safety and the exploratory efficacy assessments. Another limitation is that most patients rolled over from the SPAN-PD study voluntarily. Therefore, there is a potential enrollment bias in that people who could tolerate the drug or thought the drug was working were self-selecting to enroll in this study. Also about 30% of the patients dropped out of this extension study, the majority of these (50%) due to withdrawal of consent.

In conclusion, CVT-301 had a favorable safety profile in long-term use and did not cause worsening in pulmonary function (in agreement with earlier studies [6,7]). Patients on CVT-301 maintained improvement in achieving ON states and reducing daily OFF time, as well as PGIC assessments over 12 months.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.10.029.

Authors' roles

(1) Conception and design of the study, or acquisition of data, or analysis and interpretation of data: ESF, CHW, PAL, MK, CO, RAH.

(2) Drafting the article or revising it critically for important intellectual content: ESF, CHW, PAL, MR, MK, AL, JQ, CO, RAH.

(3) Final approval of the version to be submitted: ESF, CHW, PAL, MR, MK, AL, JQ, CO, RAH.

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ESF: Served on advisory boards for Acadia, Acorda Therapeutics, Adamas, US WorldMeds, and Teva.

CHW: Research support (Sanofi, Biogen, Roche). Consulting fees from Acorda, Amneal, Acadia, Impel, Kyowa, Mitsubishi, Neurocrine. Honoraria for speaking engagements from Acadia, Acorda, Adamas, Amneal, US WorldMeds.

PAL: Consulting fees from Abide, Acorda Therapeutics, Biogen, Britannia, Cavion, Denali, Intec Pharma, Jazz Pharmaceuticals, Lundbeck, Neurocrine, NeuroDerm, Prexton, Revance, Sage, SynAgile, Titan, and US WorldMeds; lecture fees from Acadia Pharmaceuticals, Lundbeck, US WorldMeds; research grant support from Acorda Therapeutics, Adamas Pharmaceuticals, Biotie Therapies, Lundbeck, Michael J. Fox Foundation, Parkinson Study Group, Pharma 2 B, Revance, Roche, Sunovion, and US WorldMeds; and compensation for services as editor-in-chief of *Clinical Neuropharmacology*.

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