Parkinsonism and Related Disorders 71 (2020) 4–10

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study

Donald G. Grosset[a,*], Rohit Dhall[b], Tanya Gurevich[c], Jan Kassubek[d], Werner H. Poewe[e], Olivier Rascol[f], Monika Rudzinska[g], Jennifer Cormier[h], Alexander Sedkov[h], Charles Oh[h]

[a] Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK
[b] Department of Neurology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[c] Neurological Institute Tel-Aviv Medical Center, Sourasky School of Medicine and Sagol School of Neuroscience, Tel-Aviv University, Israel
[d] Department of Neurology, University of Ulm, Ulm, Germany
[e] Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
[f] Clinical Investigation Center CIC1436, Department of Clinical Pharmacology and Neuroscience, NS-Park/FCRIN Network; CHU de Toulouse, Université de Toulouse3, INSERM, Toulouse, France
[g] Department of Neurology, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[h] Acorda Therapeutics, Inc., Ardsley, NY, USA

ARTICLE INFO

Keywords:
Inhaled levodopa
Motor fluctuations
Off periods
Safety
Efficacy

ABSTRACT

Introduction: CVT-301 is an orally inhaled levodopa therapy approved for the intermittent treatment of OFF episodes in Parkinson's disease patients who are taking a standard oral levodopa regimen. This open-label, randomized, controlled study over 12 months characterizes the safety, including pulmonary safety, of CVT-301 84 mg (nominal respirable levodopa fine-particle dose, 50 mg).

Methods: Patients experiencing motor fluctuations were randomized 2:1 to CVT-301 or an observational cohort (OC) receiving oral standard of care. Pulmonary safety was assessed using spirometry and carbon monoxide diffusion capacity (DL_{CO}). Exploratory efficacy endpoints, assessed only for CVT-301, included change in Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), patients achieving ON within 60 min and remaining ON at 60 min, Patient Global Impression of Change (PGIC) scale, and total daily OFF time.

Results: Of 408 patients randomized, 310 completed the study (204 in CVT-301 and 106 in OC). Mean 12-month changes from baseline for CVT-301 were −0.105 L (FEV_1) and −0.378 mL/min/mm Hg (DL_{CO}), and for OC were −0.117 L and −0.722 mL/min/mm Hg, respectively. Between-group comparisons were not statistically significant. For FEV_1/FVC the 12-month change was −0.3 and −1.6, respectively, which was a significant between-group difference. However, between-group differences were not significant at 3 and 9 months and all changes from baseline were small (< 2.0%). UPDRS-III scores improved from predose to 60 min postdose at all assessments; 80%–85% of patients switched ON within 60 min and remained ON; and > 75% reported improvement in PGIC. OFF time decreased by 1.32–1.42 h/day.

Conclusion: CVT-301 84 mg induced no clinically significant differences in pulmonary function compared with the OC. Improvements in motor scores, OFF time, and patient-reported outcomes support clinical efficacy for up to 12 months.

1. Introduction

Levodopa (LD) administered orally with a dopa decarboxylase inhibitor (DDI) such as carbidopa is the most effective treatment for managing the motor symptoms of Parkinson's disease (PD) [1–3]. However, ON-OFF fluctuations become increasingly frequent with chronic LD exposure and disease progression [3–5].

CVT-301 (Inbrija™) is a self-administered, orally inhaled therapy approved for the intermittent treatment of OFF-period symptoms in patients with PD who are taking an oral carbidopa/LD regimen [6–8]. Inhaled LD, which bypasses the gastrointestinal route, enters the bloodstream rapidly and predictably [8]. In a double-blind, placebo-controlled phase 3 study in patients on standard PD therapy, CVT-301 84 mg (nominal respirable LD fine-particle dose, 50 mg) significantly

* Corresponding author. Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF, United Kingdom.
E-mail address: donald.grosset@glasgow.ac.uk (D.G. Grosset).

https://doi.org/10.1016/j.parkreldis.2019.12.012
Received 9 May 2019; Received in revised form 20 September 2019; Accepted 20 December 2019

improved the Unified Parkinson's Disease Rating Scale Part III (motor) (UPDRS-III) score at 30 min postdose at week 12 compared with placebo [7]. A greater percentage of patients treated with CVT-301 (58%) experienced and maintained an ON response through 60 min after dosing compared with placebo (36%) [7]. In 2 phase 2 studies, pulmonary safety and tolerability of CVT-301 were evaluated in PD patients experiencing motor fluctuations [9,10]. Spirometry assessments were within normal ranges at screening, and showed no significant difference between CVT-301 and placebo over 4 weeks [10].

Pulmonary safety of an inhaled therapy is important given expectation of long-term use for management of PD OFF symptoms. This 12-month, open-label, randomized, observational cohort (OC)-controlled study of PD patients experiencing motor fluctuations was designed primarily to evaluate the long-term pulmonary safety of CVT-301 84 mg as an adjunct to an oral DDI/LD therapeutic regimen for up to 12 months, while supporting, via an open-label, uncontrolled approach, previous efficacy and tolerability results.

2. Methods

2.1. Study population

Eligibility criteria included idiopathic PD, diagnosed after age 30 years; modified Hoehn and Yahr stage [11] 1 to 3 (in the ON state); ≥2 h of average daily OFF time (excluding early-morning OFF time); taking a stable oral DDI/LD regimen with ≥3 daily doses and total daily LD dose ≤1600 mg; UPDRS-III improvement ≥25% from OFF to ON at screening; Mini-Mental State Examination [12] score ≥25; no dyskinesia interfering with study procedures; and no chronic respiratory disease within the last 5 years. Patients had to be able to perform spirometry in both ON and OFF states and to have FEV_1 (forced expiratory volume in 1 s) ≥50% of predicted volume, and FEV_1/FVC (forced vital capacity) ratio > 60% in the ON state at screening. Patients were CVT-301-naïve, except for 3 patients who were enrolled from phase 2 studies under an early version of the protocol.

The study (NCT02352363) was conducted at 8 sites in the United States, 50 sites in Europe and 4 sites in Israel, and was performed in accordance with the Declaration of Helsinki. All sites received institutional review board approval, and patients provided written informed consent.

2.2. Assessments

The primary objective of this study was to characterize pulmonary safety, as assessed by spirometry, over a 12-month period in CVT-301-treated patients. The primary outcome measures were FEV_1, FVC, FEV_1/FVC ratio, and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) assessed over the 12-month period, with a negative change indicating a decline in pulmonary function. While FEV_1, FVC, and FEV_1/FVC ratio allow for determination of obstructive or restrictive lung disease, DL_{CO} is a measure of gas exchange across the alveolar-capillary membrane [13].

Nonpulmonary safety assessments included dyskinesia occurrence and severity (mild, moderate, or severe) during the 60-min postdose period at each visit as recorded by the investigator. Other safety assessments were adverse events (AEs), serious AEs, clinical laboratory values, routine and orthostatic vital signs, electrocardiograms (ECGs), and physical examination. In addition, assessments of suicidality (Columbia-Suicide Severity Rating Scale [14]), somnolence (Epworth Sleepiness Scale [15]), and impulse control behaviors (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease [16]) were performed.

Exploratory efficacy assessments, performed on the CVT-301 cohort only, included UPDRS-III scores, Patient Global Impression of Change (PGIC) scale, and the occurrence of an ON state during the 60 min postdose as assessed by the investigator (a binary assessment of ON or OFF).

2.3. Study design

Eligible patients were randomized 2:1 using an interactive web response system to CVT-301 84 mg or to the OC, in which patients received standard oral PD treatment. Randomization was stratified by Hoehn and Yahr scale rating category (< 2.5 versus ≥2.5), as measured in the ON state, to balance the disease severity in each group, and by screening spirometry results (FEV_1 < 60% of predicted and FEV_1/FVC ratio < 70%, versus FEV_1 ≥60% of predicted and FEV_1/FVC ratio ≥70%). Testing was performed in accordance with the American Thoracic Society/European Respiratory Society criteria [17] before randomization.

The study included a screening period lasting up to 35 days and a treatment period of approximately 12 months, with study visits at baseline, 1, 3, 6, 9, and 12 months, plus a follow-up at a pulmonary function facility 1 month after the last visit (Fig. 1A). Spirometry and DL_{CO} assessments were performed at a dedicated pulmonary function facility within 2 weeks before baseline; at 3-, 6-, 9-, and 12-month visits; and at the follow-up visit. Pulmonary safety results for the CVT-301 group were compared with those from the OC. Spirometry and DL_{CO} assessments were performed when patients were in the ON state.

Exploratory efficacy measurements in the CVT-301 cohort were taken at baseline and months 1, 3, 6, 9, and 12. UPDRS-III assessments were performed for all patients immediately predose; and at 10, 20, 30, and 60 min postdose. Patients completed the PGIC on arrival at each visit, preferably while in the ON state. Patients also recorded in a PD diary [18] their waking ON/OFF status (time OFF, time ON without dyskinesia, time ON with non-troublesome dyskinesia, time ON with troublesome dyskinesia) and their time asleep during the 3 consecutive days before each visit. Efficacy measurements were not taken in the OC.

2.4. Dosing

Patients were trained to use the inhaler and used CVT-301 ≤ 5 times/day when they began to experience OFF-period symptoms, typically indicated by return of PD motor symptoms. For some patients, nonmotor symptoms heralded the onset of OFF periods shortly before the appearance of motor symptoms. During the study visits, patients self-administered their first dose of CVT-301 between 2 and 5 h after oral LD medication, when the patient's OFF state was recognized by both patient and investigator. The CVT-301 dose consisted of 2 capsules, each containing 42 mg LD (a nominal 25 mg respirable LD fine-particle dose), delivered sequentially using the oral breath-actuated inhaler to provide a total of 84 mg (a nominal 50 mg fine-particle dose).

Patients used CVT-301 adjunctively with their stable PD medication, as a 2-capsule (i.e., 84 mg total) dose per treated OFF period. CVT-301 was not used for treatment of early-morning OFF periods (morning akinesia) because the effects of inhaled levodopa without current intake of carbidopa were not known at the time of this study [19]. If a patient developed significant tolerability concerns, a dose reduction from 2 capsules to 1 capsule was permitted. The patient then continued to use 1 capsule per OFF period for ≥1 week. If the tolerability issue resolved, the patient could either resume taking the original 84-mg dose or could receive a 60-mg reduced-dose kit (35 mg respirable fine-particle dose). If a patient who had returned to the full 84-mg dose had another tolerability concern, the dose was reduced to 60 mg, and the patient remained on 60 mg LD for the remainder of the study. In inhaled-dosing logs, all patients recorded the number of times they used their inhaler (and the number of capsules).

Patients could continue their usual standard baseline oral PD medications throughout the study. In the CVT-301 group, however, patients were not permitted to use other “rescue” medications such as

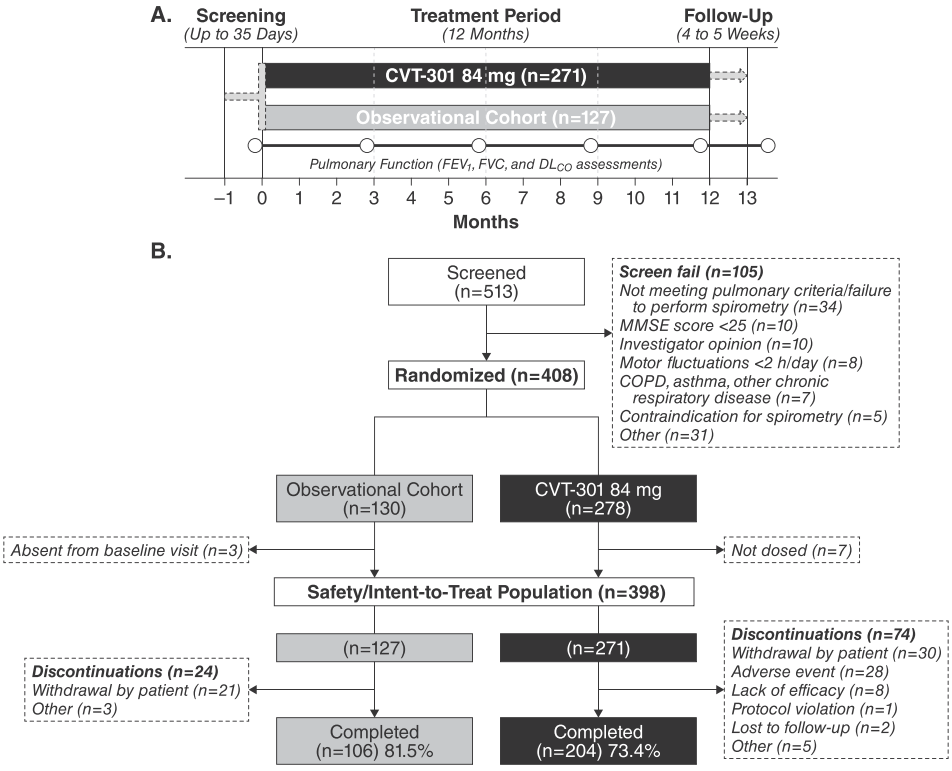

Fig. 1. Study design (A) and patient disposition (B). Study visits occurred at 0, 1, 3, 6, 9, and 12 months. COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMSE, Mini-Mental State Examination.

apomorphine or additional on-demand doses of oral LD. Patients in the OC did not use CVT-301.

2.5. Statistical analysis

The safety population was the same as the intent-to-treat population and consisted of patients who received ≥1 dose of inhaled CVT-301 as well as patients in the OC.

Changes in FEV_1, FEV_1/FVC ratio, and DL_{CO} values within each treatment group and differences between treatment groups were estimated with a prespecified mixed-model for repeated measurements (MMRM) analysis for all visits over the 12-month study period. The model included the treatment group, visit, stratification variables, and interaction between the treatment group and visit as fixed factors. Baseline spirometry value was included as a covariate. Treatment difference was assessed with a 2-sided alpha level of 0.05. A sensitivity analysis was performed using multiple imputation analysis based on application of pattern-mixture models.

For continuous efficacy variables, within-group changes from baseline were estimated using MMRM. No between-group differences were calculated because efficacy assessments were obtained only for the CVT-301 group. The model included the fixed factors of visit and the stratification variables (Hoehn and Yahr stage and screening FEV_1 and/or FEV_1/FVC). Baseline value was used as a covariate. For categorical efficacy endpoints, variables were evaluated descriptively by visit. Statistical evaluations were performed using Statistical Analysis Software (SAS®) Version 9.3 or higher (SAS Institute, Cary, NC).

2.6. Sample size selection

The sample size was selected to meet the International Council for Harmonization E1 guidelines to ensure that a minimum of 100 patients in the CVT-301 group completed 12 months of treatment [20].

3. Results

First patient was enrolled April 8, 2015, and last patient visit was May 16, 2017. Of the 513 patients screened, 408 were randomized, 278 to CVT-301 and 130 to the OC. Of the 105 screen failures, the primary reasons were failure to meet pulmonary eligibility criteria or failure to perform spirometry (34 patients, 32.4%). The study was completed by 204 patients in the CVT-301 group and 106 in the OC group (Fig. 1B). Demographic and PD baseline characteristics were similar between groups, except for mean daily LD dose, which was 874.1 (SD 348.3) mg/day for the OC and 781.9 (357.7) mg/day for the CVT-301 group (Table 1).

The mean duration of exposure was 308.9 (113) days for the CVT-301 group, with 241 patients still receiving CVT-301 at 3 months, 227 at 6 months, 212 at 9 months, and 204 at 12 months. The average number of daily doses was 2.33 (0.94) overall for CVT-301 patients. The average CVT-301 usage did not change significantly over the course of the study: usage was 2.33 doses/day (1.0) for the first 4 weeks and 2.40 doses/day (1.05) over the final 3 months. This represents a mean LD dose of 201.6 mg or 120.0 mg respirable LD fine-particle dose over the final 3 months. A total of 183 patients (67.5%) used 4 doses/day (336.0 mg total/200.0 mg fine-particle dose) at least once, and 94 patients (34.7%) used 5 doses/day (420.0 mg/250 mg fine-particle dose) at least once. Approximately 15% of all dosing days were at ≥4 doses/day. The CVT-301 dose was decreased in 11 patients (4.1%) based on tolerability concerns; of these, 6 patients (2.2%) eventually returned to either 84 or 60 mg.

3.1. Pulmonary safety

At baseline, mean FEV_1 was 2.84 L for both the CVT-301 and OC groups, while FEV_1/FVC values were 77.6 and 76.8, and mean DL_{CO} values were 23.3 and 23.7 mL/min/mm Hg, respectively. The mean (SD) change from baseline in FEV_1 at 12 months was −0.105 L (0.209) for the CVT-301 group and −0.117 L (0.214) for the OC (Fig. 2A), with

Table 1
Baseline demographics and disease characteristics.

Variable	Observational cohort (n = 127)	CVT-301 (n = 271)
Age, mean (range), years	64.2 (38–79)	63.6 (37–80)
Sex, male, %	61.4	59.4
Race, white, %	98.4	97.8
Height, mean (SD), cm	168.6 (9.4)	168.0 (8.9)
BMI, mean (range), kg/m^2	26.9 (16.2–45.9)	27.2 (17.6–44.1)
Screening spirometry, FEV_1 ≥60% and FEV_1/FVC ≥70%, %	92.9	93.4
Modified Hoehn and Yahr stage, %		
< 2.5	47.2	46.9
≥2.5	52.8	53.1
Time since PD diagnosis, mean (SD), years	9.7 (5.2)	9.0 (4.8)
Number of daily OFF periods, mean (SD)	3.7 (1.0)	3.6 (1.1)
Daily OFF time, mean (SD), hours	5.7 (2.1)	5.6 (2.1)
Duration of LD treatment, mean (SD), years	7.3 (4.6)	7.2 (4.8)
Daily LD dose, mean (SD), mg	874.1 (348.3)	781.9 (357.7)
Number of daily LD doses, mean (SD)	5.2 (1.3)	5.1 (1.5)
Screening UPDRS-III total score, mean (SD)		
OFF	38.0 (11.4)	37.8 (11.4)
ON	18.4 (9.1)	18.1 (8.9)
Other PD drug use, n (%)		
Dopamine agonists	94 (74.0)	204 (75.3)
Ropinirole	50 (39.4)	93 (34.3)
Pramipexole	31 (24.2)	65 (24.0)
Rotigotine	12 (9.4)	39 (14.4)
Piribedil	1 (0.8)	3 (1.1)
Cabergoline	1 (0.8)	0
MAO-B inhibitors	45 (35.4)	111 (41.0)
Amantadine	37 (29.1)	80 (29.5)
Tertiary amines	10 (7.9)	12 (4.4)

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LD, levodopa; MAO-B, monoamine oxidase B; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

a nonsignificant least-squares (LS) mean difference of 0.002 L (95% CI: -0.046, 0.050), $P = 0.936$. The FEV_1/FVC mean change from baseline at 12 months was 0.5 (3.8) for the CVT-301 group and −0.5 (4.0) for the OC. The LS mean change from baseline in FEV_1/FVC at 12 months was −0.3 (−1.0, 0.4) and −1.6 (−2.5, −0.8) for CVT-301 and the OC, respectively, with this change being significantly greater in the OC group, by 1.3 (0.5, 2.1), $P = 0.002$. The LS mean difference at 6 months was also significant, at 0.8 (0.00, 1.5), $P = 0.048$. However, between-group differences were not significant at the other assessment time points (3 and 9 months), and all changes from baseline were numerically small (< 2.0%). Mean change from baseline at 12 months in DL_{CO} was −0.38 (2.27) for patients in the CVT-301 group and −0.72 (2.49) for the OC (Fig. 2B), with an LS mean difference of 0.13 mL/min/mm Hg (−0.42, 0.69), $P = 0.637$. Changes from baseline between the groups were not significant at any visit. Mean spirometry values for baseline and each visit are presented in esupp Table 1.

3.2. Adverse events

Twenty-eight of 271 patients (10.3%) randomized to CVT-301 treatment withdrew from the study because of an AE (Table 2). Of these, 3 patients withdrew before administration of CVT-301, and 1 patient withdrew because of a preexisting AE of chronic lymphocytic leukemia. Therefore, 24 patients (8.9%) in the CVT-301 group experienced treatment-emergent AEs (TEAEs) that led to study withdrawal. No study drug was administered in the OC, so no patients in the OC withdrew due to a TEAE. Cough, which occurred in 3 patients, and hallucination and bronchitis, which occurred in 2 patients, were the only TEAEs that led to study withdrawal in more than 1 patient. Three patients had > 1 AE given as the reason for withdrawal: 1 had AEs of pulmonary embolism, dehydration, syncope, and rhabdomyolysis; another had tachycardia, blurred vision, dry mouth, flushing, hypertension, and bronchitis. The third patient had upper respiratory tract irritation, salivary hypersecretion, nausea, and nasal congestion. There was 1 death during the study: a patient in the CVT-301 treatment group died from drowning (anoxia), which the investigator considered to be not related to CVT-301. Serious AEs included urinary tract infection, osteoarthritis, femoral neck fracture, back pain, inguinal hernia, PD worsening, and dehydration. There were 2 serious AEs possibly related to CVT-301: pulmonary embolism and dopamine dysregulation syndrome, which occurred in 1 patient each.

The most common AEs (≥5% in any cohort) were cough, nasopharyngitis, dyskinesia, and fall (Table 2). The most common CVT-301–related AEs were cough, dyskinesia, throat irritation, and discolored sputum. Most TEAEs of cough were mild (38/43, 88.4%), and 1 event was severe. Three patients discontinued because of cough, and 28/36 (77.8%) of cough AEs started within the first 30 days of treatment.

Among CVT-301-treated patients, the examiner-reported incidence of dyskinesia during the 60-min postdose period at each clinic visit generally decreased over time, from 55 patients (20.3%) at 1 month to 35 patients (12.9%) at 12 months. Most occurrences were mild or moderate in severity, with 1–3 patients (0.4%–1.1%) experiencing severe dyskinesia at a visit. Mean UPDRS Part IV dyskinesia total scores showed no significant change (2.0 at baseline to 2.1 at 12 months). On other safety measures, there were no CVT-301–associated effects for suicidal ideation or behavior, no overall differences for impulsive-compulsive disorders compared with OC, and no worsening in sleepiness compared with OC. Orthostatic hypotension, measured predose at each visit, affected 14.5% of CVT-301 and 14.9% of OC patients at 6 months, 10.4% and 15.3% at 9 months, and 15.4% and 9.3% at 12 months. Clinical laboratory tests, physical examinations, vital signs, and ECG results were generally unremarkable and similar between cohorts.

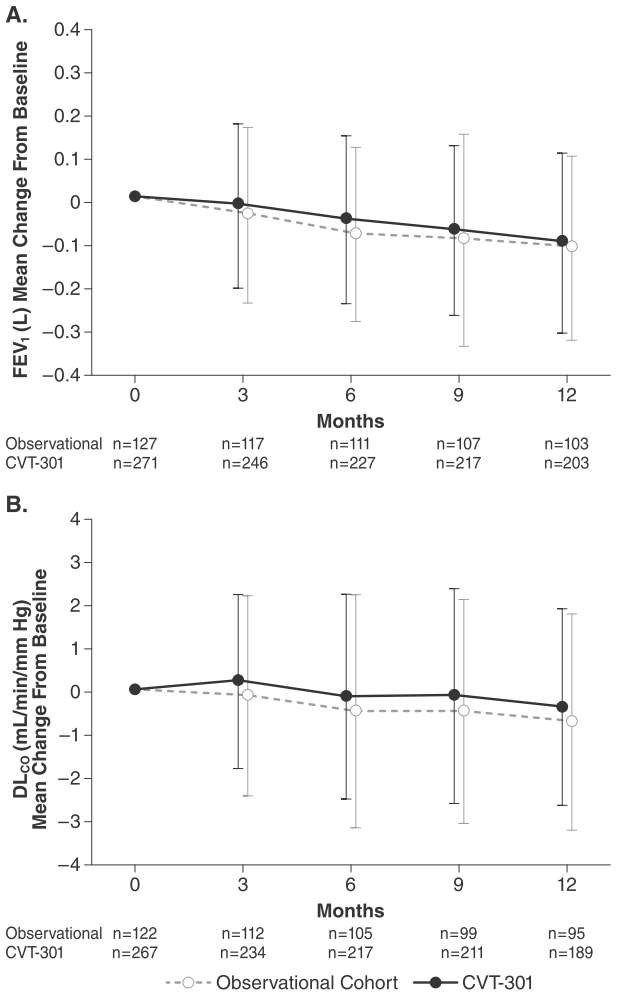

Fig. 2. Mean changes from baseline in FEV_1 (A) and DL_{CO} (B) over 12 months. Note: Error bars represent standard deviation. Time points are staggered for clarity. DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s.

3.3. Efficacy

Exploratory efficacy analysis of the change in UPDRS-III scores with CVT-301 showed maximum improvement by 30 min and was sustained through 60 min postdose (esupp Fig. 1A). Postdose mean UPDRS-III changes were consistent from months 1–12. Eighty percent to 85% of patients achieved ON within 60 min and remained ON at 60 min after a single dose of CVT-301 (esupp Fig. 1B). PD diaries showed that reductions in LS mean total daily OFF time were maintained over 12 months (esupp Fig. 1C). At months 3, 6, and 12, ≥75% of patients reported improvement in PGIC (esupp Fig. 1D). Daily ON time without dyskinesia improved from baseline at months 1 through 12 (LS mean change 1.01–1.49 h) without notable changes in daily ON time with non-troublesome or troublesome dyskinesia.

4. Discussion

This study represents the largest prospective evaluation of pulmonary function in PD patients followed for up to 12 months, and it was designed to assess the long-term safety of CVT-301. Comparable declines in FEV_1 and DL_{CO} were noticed in CVT-301 and OC groups, while FEV_1/FVC ratio declined in the OC, but not in the CVT-301 group. The annual decline in FEV_1 in healthy nonsmoking individuals is approximately 30–40 mL and is age-dependent [21]. Participants in both the CVT-301 group and the OC had a mutually consistent decrease in

Table 2
Summary of TEAEs.

	Observational cohort (n = 127)	CVT-301 84 mg (n = 271)
Any TEAEs		
Patients, n (%)	73 (57.5)	192 (70.8)
Events, n	214	654
Serious TEAEs		
Patients, n (%)	13 (10.2)	42 (15.5)
Events, n	18	61
Severe TEAEs		
Patients, n (%)	9 (7.1)	36 (13.3)
Events, n	14	57
Drug-related TEAEs		
Patients, n (%)	–	102 (37.6)
Events, n	–	209
TEAEs leading to study withdrawal		
Patients, n (%)	0	24 (8.9)
Events, n	0	35
TEAEs occurring in ≥3% patients in any group, patients (%)		
Cough	1 (0.8)	36 (13.3)
Fall	7 (5.5)	22 (8.1)
Nasopharyngitis	7 (5.5)	18 (6.6)
Dyskinesia	5 (3.9)	17 (6.3)
Upper respiratory tract infection	3 (2.4)	13 (4.8)
Back pain	4 (3.1)	12 (4.4)
Nausea	1 (0.8)	10 (3.7)
Hypertension	4 (3.1)	9 (3.3)
Sputum discolored	0	9 (3.3)
Throat irritation	0	9 (3.3)
Arthralgia	3 (2.4)	8 (3.0)
Parkinson's disease[a]	4 (3.1)	8 (3.0)
Vertigo	0	8 (3.0)
Bronchitis	4 (3.1)	7 (2.6)
Orthostatic hypotension	4 (3.1)	7 (2.6)
Influenza	4 (3.1)	4 (1.5)
Insomnia	5 (3.9)	3 (1.1)
Musculoskeletal pain	4 (3.1)	3 (1.1)

PD, Parkinson's disease; TEAEs, treatment-emergent adverse events.
[a] Worsening of PD symptoms.

FEV_1 over the 1-year period that was approximately 3 times greater than the expected decline in a non-PD population and may be due to underlying PD-related factors. The randomized OC served an important function in this study by demonstrating the lack of impact of CVT-301 administration on pulmonary function, in contrast to the contribution of the natural progression of PD. A commonly accepted minimally important difference for FEV_1 in patients with COPD is 0.1 L, and the treatment difference was −0.01 in this study [22]. No minimally important difference for FEV_1/FVC has been described. For $DL_{CO,}$ the minimally important difference in patients with COPD is 1.1 [23], whereas the treatment difference in this study was 0.34, with the CVT-301 group exhibiting a numerically smaller decline than the OC. Dry-powder inhalers have been successfully employed in the delivery of other active pharmaceutical ingredients [24], so this study shows that CVT-301 has no particular pulmonary safety risks associated with this particular inhalation system for patients in this PD population. Our data support earlier CVT-301 studies, which showed that spirometry findings were within normal ranges and were not significantly different between CVT-301 and placebo over 4 weeks [10] and 12 weeks [7]. A small proportion of screened patients (34/513, 6.6%) failed screening because they were unable to perform spirometry in both the ON and OFF states or had FEV_1 ≥50% of predicted volume and FEV_1/FVC ratio > 60% in the ON state at screening. This may have biased the study toward patients with better pulmonary function. As a comparison, the study by Hampson et al. [9] reported that 8.2% of screened patients were unable to achieve FEV_1 > 60% of predicted value and FEV_1/FVC ≥75% when ON, and an additional 3.0% were unable to perform spirometry.

CVT-301 at a dose of 84 mg was generally well tolerated and had a

safety profile consistent with previous studies of CVT-301 and of oral LD, except for mild transient cough associated with inhalation.

Exploratory efficacy measures showed improvement in UPDRS-III scores 10 min after CVT-301 administration and this was sustained for 60 min. This pattern of improvement continued over the 12-month study. Likewise, most patients achieved an ON state within 60 min postdose, and patient PD diaries recorded 1.32–1.42-h reductions in daily OFF time over the 52 weeks. These measures of efficacy were supported by the PGIC results, which showed that > 75% of patients reported improvement at each visit. A limitation of these efficacy results is the lack of a control population; the OC served as a control for pulmonary safety rather than efficacy. Also, the power calculations did not address the efficacy measures which were analyzed in an exploratory manner.

Patients were instructed not to take CVT-301 for early-morning OFF periods (first OFF period of the day), so the usage was only 2.3 doses/day, compared with the mean of 3.6 OFF periods/day observed at baseline. A separate, randomized-crossover, single-dose study has addressed the administration of CVT-301 84 mg versus placebo for treatment of early-morning OFF periods [19].

In conclusion, CVT-301 84 mg used for ≤12 months produced no clinically significant differences in pulmonary function compared with the OC. Improvements in motor scores, OFF time, and patient-reported outcomes support clinical efficacy for ≤52 weeks of treatment. Treatment of OFF periods remains an important unmet need for many patients with PD, and this study supports the previously established safety and efficacy of CVT-301 and confirms that it presents no significant pulmonary safety concerns over 12 months in this population of PD patients.

Funding sources

This study was supported by Acorda Therapeutics, Inc. Editorial assistance was provided by Robin Smith, PhD of The Curry Rockefeller Group, LLC, which was funded by Acorda. The sponsor was involved in study design, data collection and analysis, and decision to submit.

Relevant conflicts of interest/financial disclosures

DGG has received compensation for consulting services to Acorda Therapeutics, and honoraria from Bial, UCB Pharma, and GE Healthcare. RD has received research support from Acorda Therapeutics, Inc. TG has received personal compensation from AbbVie Israel and Neuroderm Ltd., and research support from Phonetica Ltd., Israeli Innovation Authority, and Parkinson's Foundation and has also been an investigator in clinical trials sponsored by Acorda Therapeutics, Inc. JK has received consulting fees as an advisory board member or honoraria as a speaker from UCB Pharma, Novartis, Bial, NeuroDerm, Teva Pharmaceuticals, Zambon, Medtronic, Desitin, AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Merz Pharmaceuticals, and Hoffmann-La Roche; and has also been an investigator in clinical trials sponsored by Acorda Therapeutics, Inc. WHP has reported personal fees from AbbVie, Allergan, AstraZeneca, Bial, Boehringer Ingelheim, Boston Scientific, GlaxoSmithKline, Ipsen, Lundbeck, Medtronic, MSD, Merck-Serono, Merz Pharmaceuticals, Neuroderm, Novartis, Orion Pharma, Teva, UCB, and Zambon (consultancy and lecture fees in relation to clinical drug development programs for Parkinson disease); and publishing royalties from Thieme, Wiley-Blackwell, Oxford University Press, and Cambridge University Press. OR has served on the advisory boards or as consultant for AbbVie, Adamas, Acorda, Addex, AlzProtect, Apopharma, AstraZeneca, Bial, Biogen, Britannia, Clevexel, Cynapsus, INC Research, Lundbeck, Merck, MundiPharma, Neuroderm, Novartis, Oxford Biomedica, Parexel, Pfizer, Prexton Therapeutics, Quintiles, Sanofi, Servier, Teva, UCB, XenoPort, and Zambon; and has received grants from Agence Nationale de la Recherche (ANR), CHU de Toulouse, France-Parkinson, INSERM-DHOS Recherche Clinique Translationnelle, MJ Fox Foundation, Programme Hospitalier de Recherche Clinique, and European Commission (FP7, H2020). MR has been principal investigator for Teva Pharmaceutical Industries Ltd., Acorda Therapeutics Inc., and Kyowa Kirin Pharmaceutical Development, Inc.; and has received research support from Medical University of Silesia and the CHDI Foundation. JC and AS were employees and stockholders of Acorda Therapeutics, Inc. at the time of the study. CO is an employee and stockholder of Acorda Therapeutics, Inc.

Authors' roles

Research project

Conception: CO, AS, JC, DGG.
Organization: CO, JC.
Execution: DGG, RD, TG, JK, WHP, OR, MR.
Data and statistical analysis: DGG, RD, TG, JK, WHP, OR, MR, JC, AS, CO.
Manuscript preparation (all drafts): DGG, RD, TG, JK, WHP, OR, MR, JC, AS, CO.
All authors approved the final paper.

Acknowledgments

The authors thank David A. Kaminsky, MD for reviewing the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.12.012.

References

[1] J.J. Ferreira, R. Katzenschlager, B.R. Bloem, U. Bonuccelli, D. Burn, G. Deuschl, E. Dietrichs, G. Fabbrini, A. Friedman, P. Kanovsky, V. Kostic, A. Nieuwboer, P. Odin, W. Poewe, O. Rascol, C. Sampaio, M. Schupbach, E. Tolosa, C. Trenkwalder, A. Schapira, A. Berardelli, W.H. Oertel, Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease, Eur. J. Neurol. 20 (1) (2013) 5–15.
[2] B.S. Connolly, A.E. Lang, Pharmacological treatment of Parkinson disease: a review, J. Am. Med. Assoc. 311 (16) (2014) 1670–1683.
[3] C.W. Olanow, M.B. Stern, K. Sethi, The scientific and clinical basis for the treatment of Parkinson disease, Neurology 72 (21 Suppl 4) (2009) S1–S136.
[4] J. Jankovic, Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations, Mov. Disord. 20 (Suppl 11) (2005) S11–S16.
[5] A.J. Lees, The on-off phenomenon, J. Neurol. Neurosurg. Psychiatry Suppl (1989) 29–37.
[6] P.A. LeWitt, R.A. Hauser, D.G. Grosset, F. Stocchi, M.H. Saint-Hilaire, A. Ellenbogen, M. Leinonen, N.B. Hampson, T. DeFeo-Fraulini, M.I. Freed, K.D. Kieburtz, A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease, Mov. Disord. 31 (9) (2016) 1356–1365.
[7] P.A. LeWitt, R.A. Hauser, R. Pahwa, S.H. Isaacson, H.H. Fernandez, M. Lew, M. Saint-Hilaire, E. Pourcher, L. Lopez-Manzanares, C. Waters, M. Rudzinska, A. Sedkov, R. Batycky, C. Oh, SPAN-PD Study Investigators, Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial, Lancet Neurol. 18 (2) (2019) 145–154.
[8] M.M. Lipp, R. Batycky, J. Moore, M. Leinonen, M.I. Freed, Preclinical and clinical assessment of inhaled levodopa for OFF episodes in Parkinson's disease, Sci. Transl. Med. 8 (360) (2016) 360ra136.
[9] N.B. Hampson, K.D. Kieburtz, P.A. LeWitt, M. Leinonen, M.I. Freed, Prospective evaluation of pulmonary function in Parkinson's disease patients with motor fluctuations, Int. J. Neurosci. 127 (3) (2017) 276–284.
[10] P.A. LeWitt, R. Pahwa, A. Sedkov, A. Corbin, R. Batycky, H. Murck, Pulmonary safety and tolerability of inhaled levodopa (CVT-301) administered to patients with Parkinson's disease, J. Aerosol Med. Pulm. Drug Deliv. 31 (3) (2018) 155–161, https://doi.org/10.1089/jamp.2016.1354 Epub 2017 Nov 21.
[11] C.G. Goetz, W. Poewe, O. Rascol, C. Sampaio, G.T. Stebbins, C. Counsell, N. Giladi, R.G. Holloway, C.G. Moore, G.K. Wenning, M.D. Yahr, L. Seidl, Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations, Mov. Disord. 19 (9) (2004) 1020–1028.
[12] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (3) (1975) 189–198.
[13] F. Al-Ashkar, R. Mehra, P.J. Mazzone, Interpreting pulmonary function tests:

recognize the pattern, and the diagnosis will follow, Clevel. Clin. J. Med. 70 (10) (2003) 866, 868, 871-873, passim.
[14] K. Posner, G.K. Brown, B. Stanley, D.A. Brent, K.V. Yershova, M.A. Oquendo, G.W. Currier, G.A. Melvin, L. Greenhill, S. Shen, J.J. Mann, The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults, Am. J. Psychiatry 168 (12) (2011) 1266–1277.
[15] M.W. Johns, A new method for measuring daytime sleepiness: the Epworth sleepiness scale, Sleep 14 (6) (1991) 540–545.
[16] D. Weintraub, S. Hoops, J.A. Shea, K.E. Lyons, R. Pahwa, E.D. Driver-Dunckley, C.H. Adler, M.N. Potenza, J. Miyasaki, A.D. Siderowf, J.E. Duda, H.I. Hurtig, A. Colcher, S.S. Horn, M.B. Stern, V. Voon, Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease, Mov. Disord. 24 (10) (2009) 1461–1467.
[17] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005) 319–338.
[18] R.A. Hauser, J. Friedlander, T.A. Zesiewicz, C.H. Adler, L.C. Seeberger, C.F. O'Brien, E.S. Molho, S.A. Factor, A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia, Clin. Neuropharmacol. 23 (2) (2000) 75–81.
[19] R.A. Hauser, S.H. Isaacson, A. Ellenbogen, B.E. Safirstein, D.D. Truong, S.F. Komjathy, D.M. Kegler-Ebo, P. Zhao, C. Oh, Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease, Parkinsonism Relat. Disord. 64 (2019) 175–180.
[20] Expert Working Group, (Efficacy) of the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Guideline for Industry: the Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-Term Treatment of Non-life-threatening Conditions, U.S. Food and Drug Administration, Rockville, MD, 1995Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life , Accessed date: 3 January 2020.
[21] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S. Ip, J. Zheng, J. Stocks, E.R.S. Global, Lung Function Initiative, Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (6) (2012) 1324–1343.
[22] P.W. Jones, K.M. Beeh, K.R. Chapman, M. Decramer, D.A. Mahler, J.A. Wedzicha, Minimal clinically important differences in pharmacological trials, Am. J. Respir. Crit. Care Med. 189 (3) (2014) 250–255.
[23] N. Horita, N. Miyazawa, R. Kojima, M. Inoue, Y. Ishigatsubo, T. Kaneko, Minimum clinically important difference in diffusing capacity of the lungs for carbon monoxide among patients with severe and very severe chronic obstructive pulmonary disease, COPD 12 (1) (2015) 31–37.
[24] A.H. de Boer, P. Hagedoorn, M. Hoppentocht, F. Buttini, F. Grasmeijer, H.W. Frijlink, Dry powder inhalation: past, present and future, Expert Opin. Drug Deliv. 14 (4) (2017) 499–512.