

Pulmonary Safety and Tolerability of Inhaled Levodopa (CVT-301) Administered to Patients with Parkinson's Disease

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Abstract

Background: CVT-301, an inhaled levodopa (LD) formulation, is under development for relief of OFF periods in Parkinson's disease (PD). Previously, we reported that CVT-301 improved OFF symptoms relative to placebo. In this study, we evaluate pulmonary function in patients treated with a single dose of CVT-301 or placebo for 3 hours, or received multiple doses/day for 4 weeks.

Methods: As part of two phase 2 studies, pulmonary safety and tolerability of CVT-301 were evaluated in PD patients experiencing motor fluctuations (≥ 2 hours OFF/day), Hoehn and Yahr stage 1–3, and forced expiratory volume in 1 second/forced vital capacity ratio $\geq 75\%$ of predicted (in ON state). In study A, patients received single doses of oral carbidopa/LD and each of the following via the inhaled route: placebo and 25 and 50 mg LD fine particle dose (FPD) CVT-301. In study B, patients received up to 3 inhaled doses/day of 35 mg (weeks 1–2) and 50 mg LD FPD CVT-301 (weeks 3–4) versus placebo. Assessments included spirometry and treatment-emergent adverse events (TEAEs).

Results: In study A, ($n = 24$) mean age \pm standard deviation was 61.3 ± 7.4 years, mean time since diagnosis was 10.5 ± 4.6 years, and mean duration of LD treatment 8.4 ± 3.7 years. Assessment of pulmonary function (predose to 3 hours postdose) showed that spirometry findings were within normal ranges, regardless of treatment groups, or motor status at screening. In study B, ($n = 86$) mean age was 62.4 ± 8.7 years, time since PD diagnosis was 9.4 ± 3.9 years, and duration of LD treatment 7.8 ± 3.9 years. Longitudinal assessment of pulmonary function over 4 weeks showed no significant difference in spirometry between CVT-301 versus placebo groups. In both studies, the most common CVT-301 TEAE was mild-to-moderate cough (study A: 21%; study B: 7% vs. 2% in placebo). Other common TEAEs in study B were dizziness and nausea.

Conclusion: Acute and longitudinal assessment of pulmonary function showed that CVT-301 treatment was not associated with acute airflow obstruction in this population. CVT-301 was generally safe and well tolerated.

Keywords: antiparkinsonian agents, dyskinesias, idiopathic, inhalation, levodopa, motor disorders, Parkinson's disease, safety, spirometry

Introduction

ORAL LEVODOPA (LD) continues to be the pharmacotherapeutic standard for managing Parkinson's disease (PD) motor symptoms.⁽¹⁾ Although LD is very effective in

alleviating the symptoms of PD, the oral route of administration can affect drug absorption.^(2–5) The variability in drug absorption from the gastrointestinal tract coupled with its short half-life and the continued loss of dopaminergic neurons can affect the plasma concentrations of LD, resulting in motor

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fluctuations over time, including OFF periods.^(6–8) Therefore, an alternative route of delivery that allows a more predictable absorption of LD with less variability is desired. Pulmonary delivery offers an alternative to oral administration of LD, as the drug will reach the epithelium that lines the alveoli capillary network almost immediately, ensuring fast absorption. The large surface area of pulmonary epithelium and the relatively low metabolic activity in the lungs are additional attributes in favor of pulmonary delivery.^(9–11)

CVT-301 is an investigational inhaled LD formulation that is being developed as a self-administered treatment for OFF periods in patients with PD who experience motor fluctuations with their existing LD regimen. CVT-301 bypasses the challenges associated with an oral route of administration of LD such as the variability of gastric emptying and of gastrointestinal transport and absorption. Through pulmonary inhalation, CVT-301 may provide a rapid and more direct route to the brain for relatively small, supplemental, doses of LD that can extend the coverage produced by the oral medication. In two studies, CVT-301 improved Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination) scores obtained 10–60 minutes after dosing during an OFF period.^(12,13)

A particular concern with an inhaled formulation is pulmonary safety. Morbidity and mortality, and central or upper airway dysfunction has been described in PD patients,^(14,15) and PD may also interfere with a patient's ability to perform pulmonary function tests.⁽¹⁶⁾ This report evaluates the safety profile of CVT-301 from two phase 2 studies of patients with motor fluctuations in PD.

Materials and Methods

The safety and tolerability of CVT-301 were evaluated in two randomized, double-blind, placebo-controlled studies: a phase 2a study (NCT01617135 [study A])^(12,13) and a phase 2b study (NCT01777555 [study B]).⁽¹³⁾

Patients

Patient selection criteria for study A included: diagnosis of PD; age 30–80 years (inclusive); Hoehn and Yahr stage 1–3 in the ON state and experiencing ≥ 2 hours of OFF time per waking day; showing acceptable LD responsiveness; with a forced expiratory volume in 1 second (FEV_1) $>70\%$ of that predicted for race, age, sex, and height; and with an FEV_1/FVC (forced vital capacity) ratio $\geq 75\%$ of predicted in the ON state.

For study B, the selection criteria were similar to those for the patients in study A, with the addition of requiring a sum of UPDRS Part III score difference of $\geq 25\%$ between ON and OFF states in response to the patient's usual LD dose. The FEV_1 had to be $>60\%$ of predicted, although the FEV_1/FVC ratio requirement remained $\geq 75\%$ of predicted in the ON state.

Both studies required patients to be on a stable oral LD regimen of at least 4 times daily dosing for at least 2 weeks before screening. Other oral treatments included stable dosages of monoamine oxidase type B and catechol-*O*-methyltransferase inhibitors. Although use of dopamine agonists was permitted, apomorphine was not allowed for 2 weeks (study A) or 4 weeks (study B) before screening and during the studies. Exclusion criteria included chronic respiratory disease within the last 5 years, and clinically significant cognitive impairment (Mini-Mental State Examination score <25) for study B.

Design

Study A. This was a randomized, placebo- and active-controlled, and double-blind study in patients with PD experiencing OFF periods (Fig. 1A).⁽¹⁷⁾ The active control was a single in-clinic, open-label dose of standard oral carbidopa/LD (25/100 mg). Single in-clinic, double-blind doses of each of three inhaled treatments were then administered in randomized order on separate treatment visits: placebo, CVT-301 25 mg LD fine particle dose (FPD), and CVT-301 50 mg LD FPD. Treatment visits were separated by at least 2 days and the duration of study ranged from ~ 6 to 12 weeks. Each treatment was administered during an OFF period at least 4 hours after each patient's usual morning dose of oral carbidopa/LD (and breakfast at home) (Fig. 1A). Spirometry was performed for all patients at screening (in both ON and OFF states) and at each treatment visit, before dosing, and at 60 and 180 minutes postdose.

Study B. This was a randomized, double-blind, placebo-controlled study for the treatment of up to three OFF periods per day in patients with PD.⁽¹⁸⁾ After screening, the patients were randomized in a 1:1 scheme to 4 weeks of at-home, double-blind use of inhaled CVT-301 or placebo up to three times per day, as needed for OFF periods. Subjects were instructed to administer inhaled medication as needed (up to a maximum of three OFF periods) when their OFF symptoms reemerged, before their next scheduled dose of oral LD. For weeks 1 and 2, the treatment was inhaled placebo or CVT-301 35 mg LD FPD (dose level 1). After 2 weeks, the CVT-301 dose was escalated to 50 mg LD FPD (dose level 2) (Fig. 1B).

Spirometry was performed during screening in both ON and OFF states and subsequently during an ON state at each study visit (before dosing) and at the follow-up safety visit.

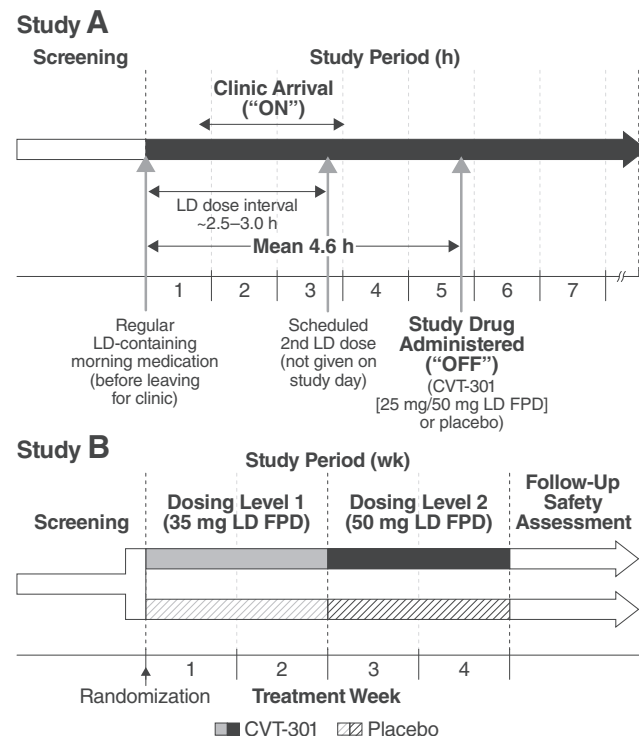


FIG. 1. Study designs. FPD, fine particle dose; LD, levodopa.

In addition, spirometry determinations were performed immediately predose and postdose at 15, 30, and 60 minutes following the first in-clinic administration of CVT-301 35 mg LD FPD or placebo and predose and 60 minutes postdose after the administration of 50 mg LD FPD or placebo.

CVT-301. CVT-301 was delivered to the lung using a 5-inch long, single-capsule-based, breath-actuated inhaler that uses the ARCUS[®] pulmonary delivery system.⁽¹⁹⁾ CVT-301 is composed of 90% LD, 8% dipalmitoyl phosphatidylcholine (DPPC), and 2% sodium chloride (NaCl). In study A, CVT-301 was supplied in size 00 hypromellose (hydroxypropyl methylcellulose or HPMC) capsules, each with a nominal fill weight of 28 mg designed to deliver an estimated 12.5 mg LD FPD to the lung. To provide the 25 mg LD FPD used in study A, two capsules were required per administration. In study B, CVT-301 was supplied in size 00 HPMC capsules, each at a nominal fill weight of 32 mg CVT-301 (27.6 mg LD per capsule) designed to deliver an approximate FPD of 17.5 mg LD to the lung per capsule inhalation. For dose level 1, two CVT-301 capsules (delivering ~35 mg LD FPD) were inhaled at each administration, and for dose level 2, three CVT-301 capsules (delivering ~50 mg LD FPD) were inhaled.

For administration, the capsule was placed into the inhaler and punctured during a simple actuation process, after which the patient inhaled the contents of the encapsulated CVT-301 through the mouthpiece. CVT-301 and placebo capsules were identical in appearance. The placebo consisted of 80% DPPC and 20% NaCl in study A and 100% lactose in study B. The inhaled placebo was intended to mask any sensation associated with dry powder inhalation to reduce potential patient- and rater-based biases on motor function-related endpoints. The placebo was supplied in size 00 HPMC capsules, each with a nominal fill weight of 10 mg.

With each inhalation, patients were instructed to take a single deep, comfortable breath followed by a breath hold of ~5 seconds after administration of each capsule. For the purposes of timing study assessments, time 0 was defined as the time of the start of the final breath hold (second 1 of the ~5-second breath hold) with the last capsule of inhaled study treatment administered during a dosing visit. In most cases, a single inhalation inhaled the whole contents of the capsule, however, if the capsule needed to be reinhaled, time 0 was at the end of the reinhalation administration.

The inhaler device is designed to be able to be used in low dexterity situations such as experienced by a PD patient during an OFF period.

Safety measures

Safety was assessed by adverse events (AEs), treatment-emergent AEs (TEAEs), changes in vital signs, clinical chemistry parameters, spirometry, and electrocardiography.

Spirometry was performed under guidelines specified by the Third National Health and Nutrition Examination Survey,⁽¹⁸⁾ the American Thoracic Society (ATS), and the European Respiratory Society (ERS).⁽²⁰⁾ Spirometry values (FEV₁, FVC, and the FEV₁/FVC ratio) were obtained from each patient's best effort, predefined as the acceptable effort yielding the highest sum of FEV₁ and FVC. All spirometry data were reviewed according to ATS/ERS quality standards. The ATS/ERS criteria require that at least 3 of the

patient's efforts be acceptable, including an exhalation lasting at least 6 seconds, and that two be repeatable, as shown by a difference of <0.15 L between the two FEV₁ values and between the two FVC values. Spirometry was performed by trained and qualified personnel using standardized equipment (6800 Fleisch Pneumotach; Vitalograph, Inc., Lenexa, KS).⁽¹³⁾

Statistical analysis

Safety measures were assessed descriptively for TEAE incidence and spirometry results. The statistical significance between CVT-301 and placebo groups was assessed using a mixed model for repeated measurements.

Ethics

Both studies were conducted in accordance with the principles originating in the Declaration of Helsinki, Good Clinical Practices, and local regulatory requirements. The study protocols and informed consent forms were approved by independent ethics committees and institutional review boards, and all patients provided written informed consent.

Results

Patient characteristics

The baseline characteristics of the patients in the two studies are summarized in Table 1. In study A, 27 patients were screened and 24 were randomized and treated. One patient did not fulfill 2 of the study dosing visits and was dropped from the completer population; 23 patients completed the study.⁽¹⁷⁾

In study B, 134 patients were screened, 89 were randomized, 86 dosed, and 75 completed the study. At baseline, 24 patients from the placebo (56%) and 26 patients from CVT-301 group (61%) had dyskinesia. Six randomized and dosed patients withdrew consent, one was lost to follow-up, and four withdrew, one from the CVT-301 treatment group and three from the placebo group, due to AEs of painful respiration, bradykinesia, chest pain, and wrist fracture.⁽¹³⁾

Pulmonary function

In study A, spirometry parameters showed that predose FEV₁, FVC, and FEV₁/FVC ratios were generally similar when comparing ON and OFF states (Table 2). Evaluation of mean changes from predose to postdose in FEV₁, FVC, and FEV₁/FVC ratio showed that the number of patients with >10% reduction in FEV₁ or FVC following CVT-301 treatments ($n=9$) was similar to the number reported following active oral carbidopa/LD ($n=6$) or placebo ($n=8$) treatments. Figure 2 shows the percent changes in FEV₁ and FEV₁/FVC from predose to 60 and 180 minutes postdose. Maximum percent reductions in FEV₁ at 60 minutes postdose for oral carbidopa/LD, placebo, and CVT-301 treatments were -22, -32, and -9, respectively; at 180 minutes the FEV₁ reductions were -30, -14, and -22, respectively.

In study B, 77% (854 out of 1109) of spirometry measurements met ATS criteria, regardless of whether patients were in the ON or OFF state. The most common reason for failure to meet ATS quality criteria was the inability to

TABLE 1. PATIENT BASELINE CHARACTERISTICS

Characteristic	Study B	
	CVT-301 group (n=43)	Placebo group (n=43)
	<i>Study A</i>	
	<i>All treated patients (n=24)</i>	
Age, years		
Mean (SD)	61.3 (7.4)	62.0 (8.4)
Median [range]	61 [41–75]	62 [37–77]
Sex, n (%)		
Male	19 (79.2)	25 (58.1)
Female	5 (20.8)	18 (41.9)
Race, n (%)		
White	24 (100.0)	41 (95.3)
Other	0	2 (4.7)
Time since PD diagnosis, months		
Mean (SD)	126.1 (55.5)	108.2 (46.0)
Median [range]	121.5 [29–245]	99 [38–254]
Duration of LD treatment, months		
Mean (SD)	100.6 (43.8)	91.5 (45.6)
Median [range]	91.5 [9–175]	85 [24–254]
OFF time, hours/day, by self-report		
Mean (SD)	4.2 (1.8)	3.6 (1.5)
Median [range]	4.0 [2–8]	3 [2–10]
OFF time, hours/day, PD diary data ^b		
Mean (SD)	NA	5.7 (2.2)
Median [range]		5.5 [2.2–11.4]
LD total daily dosage, mg		
Mean (SD)	703.6 (435.7)	687 (276)
Median [range]	575 [200–2100]	688 [250–1800]
LD doses/day		
Mean (SD)	6.0 (2.6)	5.6 (1.4)
Median [range]	5 [4–14]	5 [4–9]

^an=42.^bThree-day average, including early-morning OFF time.

LD, levodopa; NA, not available; PD, Parkinson's disease; SD, standard deviation.

perform a repeatable effort, and there were no differences in the reasons for failure between ON and OFF states.

FEV₁, FVC, and FEV₁/FVC ratios were within normal ranges and did not differ significantly between the ON and OFF states at screening (and no CVT-301 treatment). The mean change from predicted FEV₁ (95% confidence interval) ON-OFF state difference was -1.4% (-3.7, 0.9). For FVC, the difference was -0.3% (-2.0, 1.5), and for the FEV₁/FVC ratio, the difference was -1.1% (-2.0, -0.1).⁽²¹⁾

There was no evidence of adverse effects on lung function when comparing spirometry parameters (FEV₁, FVC, and FEV₁/FVC) at predose versus postdose with CVT-301 treatment. Nor were there any significant differences in

these parameters between CVT-301 and placebo over 4 weeks of double-blind treatment, as shown in Table 3; maximum reductions in FEV₁ for CVT-301 versus placebo were -0.17 L versus -0.16 L, respectively.

Safety and tolerability

In both studies, there were no deaths and the most common CVT-301 TEAE was cough. The cough was generally transient and concurrent with capsule inhalation. In study A, none of the patients with cough had any other respiratory symptoms reported as TEAEs, nor experienced any changes in respiratory rate or spirometry: all resolved promptly and without treatment or intervention.⁽¹⁷⁾

TABLE 2. STUDY A: SPIROMETRY DATA FOR PREDOSE PATIENTS IN ON AND OFF STATES (N=24)

Parameter, mean (SD) [range]	Motor state	
	ON (n=191)	OFF (n=42)
FEV ₁ , L	3.114 (0.874) [1.50–5.61]	2.970 (0.982) [1.38–5.27]
FVC, L	3.920 (1.158) [1.83–10.10]	3.849 (1.127) [2.06–6.62]
FEV ₁ /FVC, %	80.12 (7.83) [31.0–97.0]	76.92 (9.35) [34.0–90.8]

n refers to number of measurements.

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

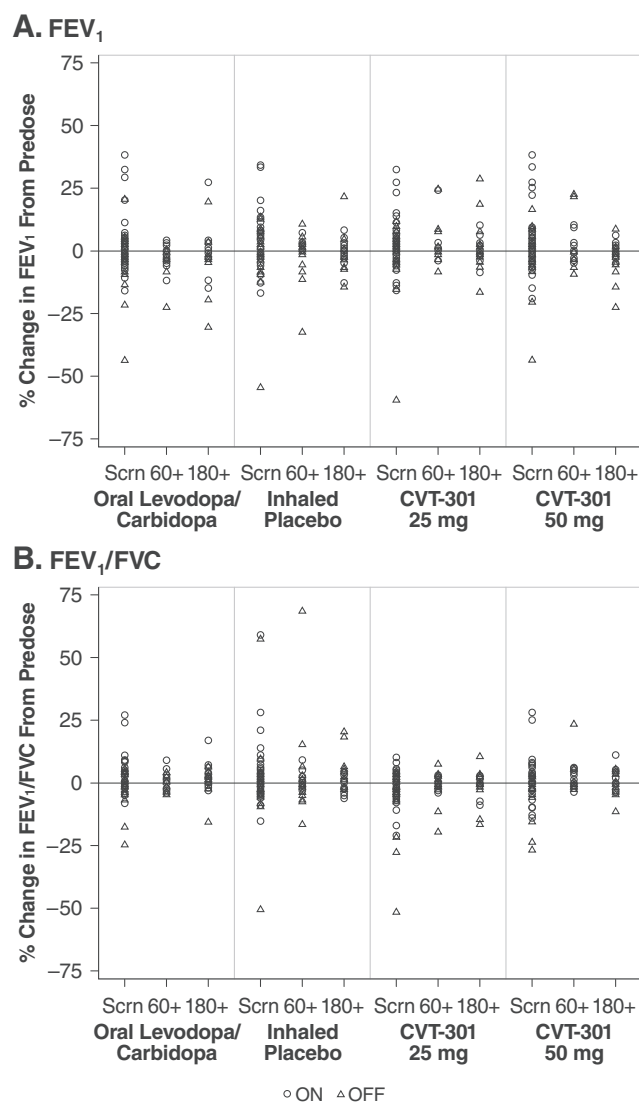


FIG. 2. Study A: Changes in lung function parameters for active control, placebo, and CVT-301 patients from predose to 180 minutes postdose. Each point represents an individual patient in an ON or OFF state. One patient was excluded from the analysis because of poor spirometry in the OFF state at screening, resulting in an inaccurate FEV₁. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Scrn, screening.

Safety and incidence of TEAEs of study B have been reported previously by LeWitt et al.⁽¹³⁾ The most commonly reported TEAEs for CVT-301 were dizziness, cough, and nausea (in 3 patients [7%] each). There were five cough events in total; one event for the placebo group and four for the CVT-301 groups. All AEs of cough were mild, unrelated to dose, and none led to withdrawal or dose modification. There were no AEs of dyspnea, wheezing, or bronchospasm. Dyskinesia was reported as a TEAE in one patient in the placebo group and one patient in the 50-mg CVT-301 group. No patients in either treatment group withdrew due to dyskinesia. Although one patient in the placebo group had dose reduction because of dyskinesia, there was no reporting of dyskinesia-related dose reduction in the CVT-301 group.

Discussion

Previously, we reported that CVT-301 provided improvement in OFF symptoms, with UPDRS Part III scores showing a treatment effect compared with placebo as early as 10 minutes, the first assessment time point.^(13,17) In this report, we discuss the pulmonary function as part of a safety evaluation of patients treated with CVT-301 or placebo.

Study A, which used spirometry to assess acute pulmonary function from predose to 3 hours postdose with CVT-301 or placebo, showed that lung function did not differ between motor states, nor between CVT-301 and placebo groups. In addition, the number of patients who experienced a 10% reduction in FEV₁ or FVC at any time point postdose was similar between all treatment groups.

It is interesting to note that there were some patients who experienced changes in FEV₁ >20% or more, and that this was irrespective of their treatment. The observed fluctuations in FEV₁ appeared to be effort-related, which may be due to the disease itself, as PD exacerbates age-related loss of respiratory muscle strength and rigidity and bradykinesia of thoracic musculature.^(16,22,23) A precise link between PD and respiratory dysfunction, however, has not been described. This issue may also represent a limitation for the interpretation of the present study.

In an earlier report, Hampson et al.,⁽²¹⁾ using spirometry data from study B, evaluated the pulmonary function of all the patients during the screening process and longitudinally for those patients taking placebo. They noted that the mean spirometry results at screening were within normal ranges

TABLE 3. STUDY B: LONGITUDINAL SPIROMETRY DATA FROM BASELINE TO WEEK 4 FOR CVT-301 AND PLACEBO

		FEV ₁ (L)	FEV ₁ (% predicted)	FVC (L)	FVC (% predicted)	FEV ₁ /FVC (%)
Placebo	Baseline mean ± SD [range] (n = 43)	2.86 ± 0.66 [1.31 to 4.11]	89.2 ± 17.4 [59.6 to 155.2]	3.63 ± 0.84 [1.68 to 5.18]	85.4 ± 15.5 [57.3 to 137.0]	79.1 ± 5.9 [55.0 to 89.0]
	Estimated change from baseline to week 4 [95% CI]	-0.05 [-0.16 to 0.07]	-2.1 [-5.7 to 1.5]	-0.07 [-0.20 to 0.06]	-2.2 [-5.4 to 1.1]	-0.6 [-1.7 to 0.5]
CVT-301	Baseline mean ± SD [range] (n = 43)	2.64 ± 0.60 [1.59 to 3.79]	88.7 ± 10.9 [63.1 to 112.5]	3.35 ± 0.74 [2.06 to 4.79]	85.7 ± 10.3 [63.2 to 116.5]	78.8 ± 4.2 [66.0 to 89.0]
	Estimated change from baseline to week 4 [95% CI]	-0.06 [-0.17 to 0.05]	-1.3 [-4.8 to 2.3]	-0.07 [-0.19 to 0.06]	-0.9 [-4.0 to 2.3]	-1.1 [-2.1 to 0.0]
CVT-301 vs. Placebo	Estimated difference at week 4 [95% CI]	-0.01 [-0.15 to 0.12]	0.9 [-3.3 to 5.0]	0.00 [-0.15 to 0.16]	1.3 [-2.6 to 5.1]	-0.5 [-1.6 to 0.7]

CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

and were not dependent on motor state (ON vs. OFF). Based on the findings, the authors concluded that it is feasible to obtain longitudinal spirometry measurements of acceptable quality (ATS criteria) in PD patients with motor fluctuation.

In this report, using all the patients in study B, we show that longitudinal spirometry data obtained from a majority (77%) of patients were of acceptable ATS-quality, regardless of treatment or motor state. Consistent with the acute spirometry findings from study A, there were no significant differences in FEV₁, FVC, and FEV₁/FVC ratios between those treated with CVT-301 versus inhaled placebo over 4 weeks of treatment as shown in Table 2. The FEV₁/FVC ratio, a measure of potential airway obstruction, did not change appreciably from baseline, suggesting that CVT-301 treatment was not associated with any evidence of acute airflow obstruction.

Inhalation of the placebo or CVT-301 particles from the inhaler produced no significant changes in lung function parameters over the duration of the study, and there were no AEs such as dyspnea, wheezing, or bronchospasm. The TEAEs of cough were generally mild in study A (70% were mild and 30% were moderate) and were experienced by 25% of patients. In study B, however, despite having a considerably longer exposure to inhalation, the number of cough TEAEs was fewer, affecting only 7% of patients (five events in total).

In conclusion, in this population of patients treated with CVT-301 pulmonary parameters did not vary significantly between ON and OFF states at screening, or over the one month of treatment with drug or placebo. Common AEs with CVT-301 were cough, dizziness, and nausea. Treatment with CVT-301 did not increase the incidence of dyskinesia as a reported TEAE.

Acknowledgments

This study was supported by Civitas Therapeutics, Inc., now wholly owned by Acorda Therapeutics, Inc. Editorial assistance was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC, and this assistance was funded by Acorda Therapeutics, Inc.

Author Disclosure Statement

P.A.L. has received compensation for advisory services, consulting, research grant support, or speaker honoraria from AbbVie, Acadia, Acorda Therapeutics, Inc., Adamas, Biogen Idec, Biotie, Cynapsus, Depomed, Impax, Insightec, Intec, International Parkinson's Disease and Movement Disorders Society, Ipsen, Kyowa, Lundbeck, Luye, Michael J. Fox Foundation for Parkinson's Research, NeuroDerm, Noven, Parkinson Study Group, Pfizer, Pharma 2B, ProStrakan, SynAgile, Teva, Tremor Research Group, UCB, U.S. WorldMeds, World Parkinson Congress, and XenPort.

R.P. has received compensation for advisory services, consulting, research grant support, or speaker honoraria from AbbVie, Acadia, Acorda Therapeutics, Inc., Acorda/Civitas, Adamas, Avid, Biotie, Boston Scientific, Cynapsus, Kyowa, Lundbeck, Medtronic, Neurocrine, NIH/NINDS, NPF, Parkinson Study Group, Pfizer, Sage, St Jude Medical, Teva Neuroscience, UCB, and U.S. WorldMeds.

A.S., A.C., and R.B. are employees and stockholders of Acorda Therapeutics, Inc. H.M. was an employee of Acorda

Therapeutics, Inc. at the time of study and during the development of this article.

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Received on November 2, 2016
in final form, August 17, 2017

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