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To cite this article: Neil B. Hampson, Karl D. Kieburtz, Peter A. LeWitt, Mika Leinonen & Martin I. Freed (2017) Prospective evaluation of pulmonary function in Parkinson's disease patients with motor fluctuations, *International Journal of Neuroscience*, 127:3, 276-284, DOI: [10.1080/00207454.2016.1194274](https://doi.org/10.1080/00207454.2016.1194274)

To link to this article: <http://dx.doi.org/10.1080/00207454.2016.1194274>



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Accepted author version posted online: 26 Jun 2016.
Published online: 27 Jun 2016.



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ORIGINAL ARTICLE

Prospective evaluation of pulmonary function in Parkinson's disease patients with motor fluctuations

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Background. Spirometry patterns suggesting restrictive and obstructive pulmonary dysfunction have been reported in Parkinson's disease (PD). However, the patterns' precise relation to PD pathophysiology remains unclear. **Purpose/Aim.** To assess ON- versus OFF-state pulmonary function, the quality of its spirometric evaluation, and the quality of longitudinal spirometric findings in a large sample of PD patients with motor fluctuations. **Methods.** During a placebo-controlled trial of an inhaled levodopa formulation, CVT-301, in PD patients with ≥ 2 h/d of OFF time, spirometry was performed by American Thoracic Society (ATS) guidelines at screening and throughout the 4-week treatment period. **Results.** Among 86 patients, mean motor impairment during an OFF state at screening was moderately severe. However, mean spirometry results at screening were within normal ranges, and in a mixed model for repeated measures (MMRM), the results at screening were not dependent on motor state (ON vs. OFF). In the placebo group ($n = 43$), 76% of ON-state and 81% of OFF-state examinations throughout the study met ATS quality metrics, and in an MMRM analysis, mean findings at these patients' arrivals for treatment-period visits showed no significant 4-week change. Across all 86 patients, flow-volume curves prior to any study-drug administration showed only a 3% incidence of "sawtooth" morphology. **Conclusions.** In PD patients with motor fluctuations, longitudinal spirometry of acceptable quality was generally obtained. Although mean findings were normal, about a quarter of spirograms did not meet ATS quality criteria. Spirogram morphology may be less indicative of various forms of respiratory dysfunction than has previously been reported in PD.

KEYWORDS: pulmonary function, spirometry, Parkinson's disease, levodopa, CVT-301

Introduction

In patients with Parkinson's disease (PD), characteristic clinical features such as rigidity and bradykinesia may impair the tone, contractility, and coordination of thoracic musculature, affecting respiratory mechanics and pulmonary function [1]. Indeed, respiratory dysfunction can contribute to morbidity and mortality in advanced PD [2–4]. PD may also affect a patient's

ability to perform the respiratory maneuvers required for pulmonary function tests (PFTs) such as spirometry [5]. In PD patients, PFT patterns suggesting restrictive pulmonary dysfunction and central- or upper-airway obstruction have been described [1,6–9]. However, the pathophysiologic basis for differing patterns and the precise relation of each such pattern to PD motor dysfunction remain unclear [1]. Parkinsonian fluctuations in motor function [10] may further complicate the clinical interpretation of spirometry data.

The potential for OFF-episode reversal via intrapulmonary drug delivery has been the impetus for clinical studies of inhaled levodopa (LD) [11,12]. CVT-301 is an LD powder formulation for inhalation. During a phase 2b randomized, double-blind, placebo controlled, multinational, multicenter trial of CVT-301 in PD patients with motor fluctuations, spirometry was performed at screening and at each of four visits throughout a 4-week treatment period [13,14]. Here we report the pretreatment findings assessing ON- versus OFF-state pulmonary function and the quality of spirometric

Received 23 November 2015; revised 10 May 2016; accepted 23 May 2016;
publish online 24 June 2016.

*At the time of the study, Dr Freed was employed by Civitas Therapeutics (now wholly owned by Acorda Therapeutics).

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evaluation across all study participants before any exposure to study drug. We also report the longitudinal spirometric findings from the study's placebo group, who were never exposed to the active study drug, and assess the quality and reproducibility of these results.

Methods

Study participants

All patients were required to be aged 30–80 years and have idiopathic PD at a modified Hoehn and Yahr (H&Y) stage [15] of 1–3 in the ON state. Patients were also required to have recognizable, predictable OFF episodes totaling at least 2 h/d (excluding early-morning OFF time). Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores [16] were required to show a $\geq 25\%$ difference between each patient's ON and OFF states. In the ON state, each patient's forced expiratory volume during the first second (FEV₁) was required to be $>60\%$ of the value predicted by the patient's age, sex, height, and race [17], and the ratio of FEV₁ to forced vital capacity (FVC) was required to be $\geq 75\%$. The patient's PD medications were required to include oral LD/carbidopa taken at least four times daily in a regimen that had been stable for at least the 2 weeks before screening. Patients were excluded for a history of chronic respiratory disease within the preceding 5 years and for a Mini-Mental State Examination score [18] <25 .

Study design

The study included a screening period lasting 2–4 weeks, a treatment period lasting 4 weeks, and a follow-up safety visit 1 week after the end of treatment. During the screening period, spirometry was performed in each patient's ON state. At the same visit, spirometry was repeated when the patient had entered an OFF state, in the judgment of an investigator. Spirometry was performed at a subsequent screening visit only if needed for assessing eligibility. In a 1:1 randomization ratio, enrolled patients were assigned to self-administer inhaled CVT-301 or placebo as needed up to three times per day for the treatment of OFF episodes. In the active-treatment group, the dose was increased at the end of week 2. Placebo-treated patients used inhalation-grade lactose monohydrate at dose levels and a particle size selected to approximate the upper-airway powder-load deposition of the active drug and mimic the sensation of active-drug inhalation but not enter the lungs. For each study-drug dose level, the drug's use began with an in-clinic self-administration.

Patients were assessed at the visit initiating study-drug use (treatment-period baseline visit), at the end of

treatment weeks 1, 2, and 4, and at the follow-up visit. At each visit, spirometry was performed at the patient's arrival, preferably in an ON state. At the baseline visit, spirometry was also performed immediately predose (regardless of the patient's ON/OFF status) and at 15, 30, and 60 min postdose. At the end-of-week-2 visit, initiating the increased study-drug dose, spirometry was performed at arrival, predose (in an OFF state, as judged by an investigator), and 60-min postdose. In all patients, all oral PD medications were held constant throughout the study. The study was registered with ClinicalTrials.gov (identifier: NCT01777555).

Spirometry procedure

At each study site, spirometry was performed by trained and qualified personnel using standardized equipment (6800 Fleisch Pneumotach; Vitalograph, Inc., Lenexa, KS, USA) under guidelines specified by the Third National Health and Nutrition Examination Survey (NHANES III), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [5,17]. Spirometry values (FEV₁, FVC, and the FEV₁/FVC ratio) were obtained from each patient's best effort, pre-defined as the acceptable effort yielding the highest sum of FEV₁ and FVC. All spirometry data were reviewed by a central spirometry laboratory (Biomedical Systems, Inc., St. Louis, MO, USA), which provided an over-read based on ATS/ERS quality standards. The ATS/ERS criteria [5] require that at least three of the patient's efforts be acceptable (including an exhalation lasting at least 6 s) 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 morphology analyses

The shape of the flow–volume curve produced by each patient at the first treatment visit, prior to active-drug or placebo administration, was interpreted *post hoc* by a pulmonologist (NBH) blinded to the patient's treatment assignment. Each curve was given one of four classifications. “Normal” curves were those that exhibited a sharp peak in expiratory flow rate (PEFR) followed by a relatively linear decline to residual volume (Figure 1A). “Sawtooth” curves demonstrated a sawtooth shape during exhalation, typically after the PEFR (Figure 1B). This pattern has been attributed to upper-airway obstruction [6–9]. “Low PEFR, reproducible” curves had a rounded peak but were consistently reproducible (Figure 1C), as is typically seen in patients with neuromuscular weakness [6–9]. “Low PEFR, not reproducible” was applied to curves with a slow rise to peak flow, a rounded peak, and inconsistent reproducibility, suggesting poor effort, difficulty with the test maneuver, or detriments such as pain (Figure 1D).

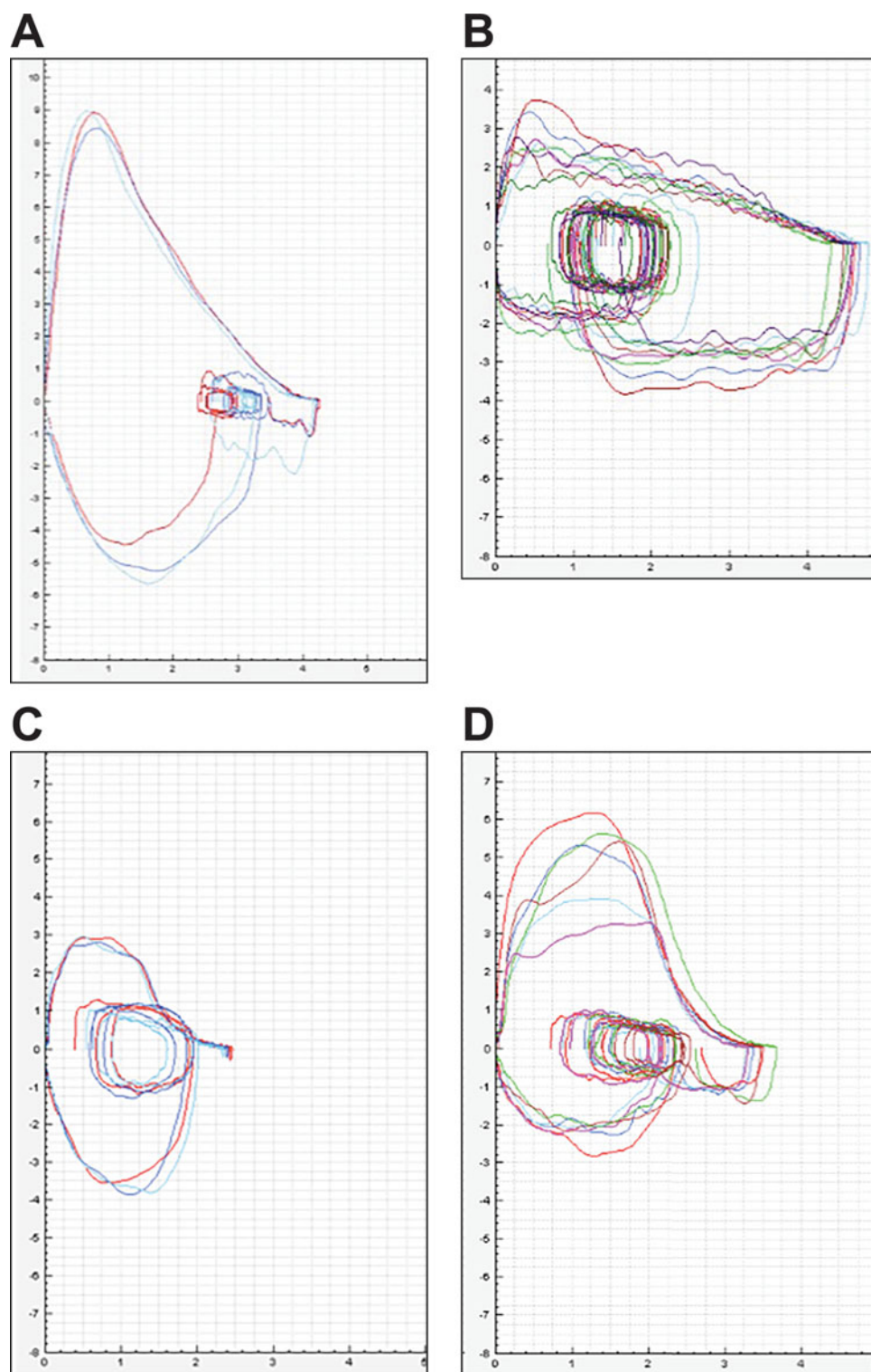


Figure 1. Examples of flow-volume curves categorized as (A) normal; (B) sawtooth; (C) low PEFR, reproducible; or (D) low PEFR, not reproducible. PEFR, peak expiratory flow rate.

Table 1. Demographic and baseline PD characteristics.

Variable	Value	
	All patients	Placebo group
<i>n</i> treated	86	43
Age (y)		
Mean (SD)	62.4 (8.7)	62.7 (9.1)
Range	37–79	43–79
Sex, <i>n</i> (%)		
Male	57 (66)	32 (74)
Female	29 (34)	11 (26)
Race, <i>n</i> (%)		
White	83 (97)	42 (98)
Asian	2 (2)	1 (2)
Other	1 (1)	0
Country, <i>n</i> (%)		
US	64 (74)	32 (74)
Italy	10 (12)	5 (12)
Serbia	8 (9)	4 (9)
Great Britain	4 (5)	2 (5)
Modified H&Y stage ^a , <i>n</i> (%)		
1.5	3 (4)	2 (5)
2	50 (58)	24 (56)
2.5	20 (23)	11 (26)
3	13 (15)	6 (14)
UPDRS Part III score, mean (SD)		
OFF state	35.8 (12.0)	36.2 (12.1)
ON state	17.5 (9.0)	18.9 (9.8)
Time since PD diagnosis (mon)		
Mean (SD)	113 (47)	117 (48)
Range	38–255	41–255
Time since emergence of fluctuations (mon)		
Mean (SD)	51 (43)	46 (40)
Range	0–254	0–150
OFF time (h/d) ^b		
Mean (SD)	5.7 (1.8)	5.8 (1.5)
Range	2.6–10.3	2.6–9.2
Number of daily OFF episodes ^c		
Mean (SD)	3.6 (1.1)	3.7 (1.0)
Range	1.0–7.0	1.7–6.0
Duration of LD treatment (mon)		
Mean (SD)	93 (46) ^d	95 (48) ^e
Range	15–254 ^d	15–243 ^e
Number of daily LD doses		
Mean (SD)	5.9 (1.9)	6.1 (2.2)
Range	4–15	4–15
LD daily dosage (mg/d)		
Mean (SD)	770 (306)	853 (315)
Range	250–1800	400–1700
Other oral PD medications, <i>n</i> (%)		
Dopamine agonists	57 (66%)	26 (61%)
MAO-B inhibitors	37 (43%)	14 (33%)
Adamantane derivatives	29 (34%)	13 (30%)
COMT inhibitors	9 (11%)	5 (12%)

COMT, catechol-O-methyl transferase; H&Y, Hoehn & Yahr; LD, levodopa; MAO-B, monoamine oxidase B; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

^aDuring an ON state.

^bFrom 3-d patient-diary data, normalized to a 16-h waking day.

^cFrom 7-d episode logs maintained during screening.

^d*n* = 85.

^e*n* = 42.

Statistical methods

Descriptive analyses are presented for ON-state versus OFF-state spirometry findings from all study participants at their screening visits; for spirometry-quality metrics in placebo-group patients at all spirometry time points; for longitudinal spirometry findings in placebo-group patients, as obtained upon their arrivals at treatment-period visits; and for flow-volume-curve morphology in all patients, as obtained prior to active-drug or placebo administration at their first treatment visit. All analyses were of observed cases, with no imputation of data.

To complement the descriptive approach, 95% confidence intervals were calculated for the ON-vs.-OFF differences at screening and for the placebo group's longitudinal changes. The ON-vs.-OFF calculations used a mixed model with repeated measures (MMRM) with H&Y stage, country, and motor state (ON vs. OFF) as fixed factors. The longitudinal-change calculations used a similar MMRM, with H&Y stage, country, and study visit as fixed factors and baseline value as a covariate. The changes themselves were estimated using contrasts.

As a *post-hoc* analysis, the variability of spirometric findings when a given parameter is measured multiple times in an individual patient was estimated by calculating the within-subject coefficient of variability (CV) for each parameter among all patients with at least two ON-state examinations before any study-drug exposure. For each patient, up to four such assessments were available: one or two at screening, plus arrival and predose assessments on the first day of treatment. The subset of examinations meeting ATS/ERS quality criteria was analyzed separately.

Results

Study participants

In all, 134 patients were screened at 20 sites, beginning in April 2013. Of the 45 screening failures, 11 (8.2% of 134) were unable to achieve an FEV₁ and/or an

FEV₁/FVC ratio meeting eligibility criteria and another 4 (3.0% of 134) were unable to perform the spirometry maneuver. The remaining 89 patients were enrolled and randomized, and 86 used at least one dose of study drug. By UPDRS Part III score [16], their mean motor impairment during an OFF state at screening was moderately severe [19]. The randomized patients included 45 patients allocated to placebo, of whom 43 used at least one dose and 36 completed the 4-week treatment period (Supplemental Figure A). The study's last patient completed treatment in January 2014. Table 1 summarizes the demographic and PD characteristics of the 86 study-drug users and the placebo-user subset, which resembled those of the full group.

Spirometry at screening

Table 2 compares the ON-state and OFF-state spirometry results obtained at the screening of all treated patients. By MMRM analysis, FEV₁ and FVC exhibited no significant difference between the patients' ON and OFF states. Although the 95% confidence interval for ON-versus-OFF difference in the FEV₁/FVC ratio did not cross zero, the mean OFF-state value showed a decrease of only 1.1% points, to 78.5% from a mean ON-state value of 79.6%. In both ON and OFF states, the variability among FEV₁ and FVC values was greater than that for the FEV₁/FVC ratio, but for all parameters, the observed mean values were well within commonly utilized normal ranges (for FEV₁ and FVC, $\geq 80\%$ of the predicted value, and for the FEV₁/FVC ratio, $\geq 70\%$) [20].

Spirometry-quality metrics

Among all spirometry measurements performed during the study in the placebo group, motor state did not predict the ability to obtain adequate spirometry. Of all ON-state examinations, 76% (238 of 314) met ATS/ERS criteria (three acceptable and two repeatable efforts as defined above, under "Spirometry procedure"). Of all OFF-state examinations, the frequency was 81% (192

Table 2. Spirometry results obtained at the screening of all treated patients. Data are presented as means with standard deviations and as estimated ON-vs.-OFF differences with 95% confidence intervals calculated using an MMRM.

Parameter	ON state (n = 86)	OFF state (n = 86)	ON-vs.-OFF estimated difference
FEV ₁ (% of predicted)	89.7 (15.5)	88.3 (15.1)	-1.4 [-3.7; +0.9]
FVC (% of predicted)	85.6 (14.9)	85.3 (13.0)	-0.3 [-2.0; +1.5]
FEV ₁ /FVC (%)	79.6 (3.6)	78.5 (5.4)	-1.1 [-2.0; -0.1]

FEV₁, forced expiratory volume during the first second; FVC, forced vital capacity; MMRM, mixed model for repeated measures.

of 236). In both motor states, the most common reason for failure was lack of repeatable efforts. This problem occurred in 41% of the deficient ON-state examinations (31 of 76) and 48% of the deficient OFF-state examinations (21 of 44). Among all examinations rejected by ATS/ERS criteria, 43% (52 of 120) had three acceptable efforts but less than two repeatable efforts. Another 41% (49) had neither three acceptable nor two repeatable efforts. The remaining 16% (19) had two repeatable efforts but lacked three acceptable efforts.

Longitudinal spirometry

Table 3 presents the spirometry results obtained from the study's placebo users upon their arrival at study visits during the 4-week treatment period. At the end of week 4, there was no significant change from baseline (the beginning of week 1) in either FEV₁, FVC, or the FEV₁/FVC ratio.

Spirogram morphology

Of the flow-volume curves obtained from patients at their first treatment visit, 45% (39 of 86) were classified as having normal morphology. Another 3% (3 curves) were classified as "sawtooth," 19% (16 curves) as "low PEF, reproducible," and 34% (29 curves) as "low PEF, not reproducible."

Within-subject variability

Among the 86 patients studied, 74 had a total of at least two ON-state spirometry evaluations prior to any study-drug exposure. For all such patients, and for the subset of 49 patients whose spirometry met ATS/ERS quality standards, Table 4 presents within-subject CVs for FEV₁, FVC, and the FEV₁/FVC ratio. Across the patients whose spirometry met the quality standards, all of the CVs were <6%. Across all of the patients, all of the CVs were <8%.

Discussion

This report represents the largest cohort of PD patients studied to date in which pulmonary function was assessed prospectively, and provides the first longitudinal spirometric data from PD patients with motor fluctuations. Furthermore, the study included same-day evaluations of PD patients in both their ON and OFF states and reviewed spirometry metrics using ATS/ERS quality standards.

A large majority of spirometric evaluations (78% overall) met the ATS/ERS criteria, confirming the ability of PD patients to perform the spirometry maneu-

Table 3. Longitudinal spirometry results in placebo-treated patients, as obtained upon their arrival for treatment-period visits. Data are presented as means with standard deviations and as estimated changes with 95% confidence intervals calculated using an MMRM (observed cases).

Time point	FEV ₁		FVC	
	Absolute value (L)	% of predicted value	Absolute value (L)	% of predicted value
Beginning of week 1 (baseline) (n = 43)	2.86 (0.66)	89.2 (17.4)	3.63 (0.84)	85.4 (15.5)
End of week 1 (n = 40)	2.81 (0.64)	87.7 (16.3)	3.59 (0.82)	84.4 (13.7)
End of week 2 (n = 39)	2.88 (0.65)	88.9 (14.9)	3.63 (0.83)	84.8 (14.3)
End of week 4 (n = 35)	2.88 (0.70)	88.6 (15.9)	3.64 (0.88)	84.6 (15.0)
Estimated change from baseline to end of week 4	-0.11 [-0.27; +0.06]	-3.1 [-7.6; +1.4]	-0.15 [-0.32; +0.03]	-3.0 [-7.0; +0.9]
FEV ₁ , forced expiratory volume during the first second; FVC, forced vital capacity; MMRM, mixed model for repeated measures.				
				FEV ₁ /FVC (%)
				79.1 (5.9)
				78.5 (6.1)
				79.5 (4.5)
				79.3 (4.9)
				-0.9 [-2.3; +0.5]

Table 4. Within-subject coefficients of variability for ON-state spirometry results prior to study-drug exposure^a.

Variable	Within-subject coefficient of variability	
	All patients (<i>n</i> = 74)	Patients with spirometry meeting ATS/ERS standards (<i>n</i> = 49)
FEV ₁	7.84%	5.39%
FVC	6.71%	4.41%
FEV ₁ /FVC	4.17%	3.17%

ATS, American Thoracic Society; ERS, European Respiratory Society; FEV₁, forced expiratory volume during the first second; FVC, forced vital capacity.

^aAmong all patients with at least two such evaluations (at screening or before study-drug dosing at the beginning of treatment week 1).

ver, regardless of their motor state. The most frequent reason for failure of a tracing to meet ATS/ERS criteria was a patient's inability to provide repeatable efforts. Overall, mean spirometry values were within normal ranges at presentation, and remained normal in patients' OFF states. Moreover, spirometry findings remained unchanged over 4 weeks of longitudinal evaluation.

In prior spirometric studies of PD patients, several patterns of abnormalities have been described. When present, the most common patterns have been characterized as restrictive pulmonary dysfunction, obstructive airflow disease, and upper airway obstruction [1,7–9,21–24]. Abnormal ventilatory control has also been described, even though respiratory flows and volumes were normal in most of the patients [25]. Most of the available studies have been cross-sectional in design. None have provided data on the intra- or inter-subject variability of repeated observations, or any ascertainment of ATS/ERS quality metrics. Three of the studies [21,23,24] presented results for both ON and OFF states. Among these studies, two described restrictive patterns, more severe in the OFF state. In one such report [23], the OFF-state findings among 12 patients showed declines of approximately 10% in both FEV₁ and FVC, to mean values of 77.9% and 76.8% of predicted, with no significant change in the FEV₁/FVC ratio. In the other report [24], LD dosing of 53 patients led to a 13% improvement in FVC, from a mean 62.8% of predicted to a mean 71.4% of predicted, with no change in the FEV₁/FVC ratio. In both studies, however, total lung capacity was not assessed. Other possible explanations for the absence of analogous findings in the current study include its stringent eligibility criteria and substantial differences from the other studies in patient characteristics such as age (at a mean of 67.7 years [23] and 53.3 years [24] in the other studies, compared with 62.4 years in the current study) and PD duration (at a mean of 14.5 years [23] and 3.1 years [24] in the other studies, compared with 9.4 years in the current study). In the third study reporting ON-state and OFF-state re-

sults [21], mean spirometry findings among 10 patients, presented only as absolute values, were higher during the OFF state, by amounts described as too small to meet ATS/ERS criteria for clinical relevance [26].

The present study excluded patients with an FEV₁ ≤60% or an FEV₁/FVC ratio <75%, patients unable to perform the spirometry maneuver, patients with chronic respiratory disease, and patients with more than moderate PD-related disability, as defined by an H&Y stage >3 during an ON state. Hence, the study's findings do not permit exploration of the pathophysiology of respiratory dysfunction in PD patients or the extent to which such dysfunction represents PD, associated physical decline, or normative aging. PD has been found to exacerbate the normative age-related loss of respiratory muscle strength [27], and PD-associated deficits in maximum inspiratory and expiratory pressures have been attributed to rigidity and bradykinesia of thoracic musculature [1]. Nevertheless, the precise causal relation of parkinsonism to respiratory dysfunction remains unknown [1]. The present findings are also limited by the absence of an active-treatment comparator. The aim here, however, was to investigate spirogram quality and reproducibility in the ON and OFF states of PD patients free of exposure to an investigational drug.

In a *post-hoc* analysis, we categorized the morphologies of the flow-volume curves produced by the patients at a point in the trial when they would have become familiar with the spirometry procedure but would not yet have received any study drug. Prior studies in smaller groups of PD patients had reported a 29% to 67% incidence of "sawtooth" morphology [6–9]. We found only a 3% incidence, undoubtedly related at least in part to differing methods of patient selection. In the current study, all patients were asymptomatic for respiratory dysfunction, regardless of flow-volume-curve morphology. Accordingly, an emphasis on the morphology seems unwarranted. Interpretation of the clinical significance of sawtoothing or other abnormalities was also limited by unavailability of comments from the spirometry tech-

nician, which might have provided insight. Of perhaps greatest significance for longitudinal spirometry in a PD population was the relatively frequent lack of test repeatability, a factor requiring consideration when planning evaluations of pulmonary function in PD studies. A lack of spirometry repeatability raises the possibility that PD patients could potentially experience difficulty with other complex PFTs, such as diffusing capacity.

Conclusions

The present study provides strong evidence that longitudinal spirometry measurements of acceptable quality can be obtained in studies of PD patients with motor fluctuations, using trained staff and strict quality controls. In contrast to prior studies, spirometry results were within normal ranges and did not differ significantly between the patients' ON and OFF states. The results also suggest that flow-volume-curve morphology, which has received much attention in the PD literature, may be less well associated with respiratory dysfunction than has been described. Some patients had difficulty performing repeatable spirometry maneuvers, implying that other complex forms of PFT might be problematic. In planning future clinical studies, these issues should be considered.

Acknowledgements

The authors wish to acknowledge Tia DeFeo-Fraulini and Amanda Gentile for expert operational assistance in the conduct of the study and Jessica Roland of Acorda Therapeutics for editorial assistance. The authors would also like to acknowledge the efforts of the CVT-301-003 Study Group for their invaluable assistance in conducting this trial.

Declaration of Interest

The authors alone are responsible for the content and writing of this paper. Neil B. Hampson worked as a noncompensated pulmonary consultant to Civitas Therapeutics during the time of the study and has no conflicts to disclose; Karl D. Kiebert is a consultant for the National Institutes of Health (NINDS), Acorda, Astellas Pharma, AstraZeneca, Auspex, Biotech, Britannia, Cangene, CHDI, Civitas, Clearpoint Strategy Group, Clintrex, Cynapsus, Intec, Isis, Lilly, Lundbeck, Medavante, Medivation, Melior Discovery, NeuroDerm, Nueromedix, Omeros, Otsuka, Pfizer, Pharm2B, Prothena/Neotope/Elan Pharmaceutical, Raptor Pharmaceuticals, Roche/Genentech, Sage Bionetworks, Serina, Staltheptides, Synagile, Teikoku Pharma, Titan, Turing Pharmaceuticals, Upsher-

Smith, US WorldMeds, Vaccinex, Voyager, and Weston Brain Institute. He received grants/research support from the Michael J. Fox Foundation, the National Institutes of Health (NEI, NINDS, NIA, NICHD), and Teva; Peter A. LeWitt served as a consultant or advisor for Acorda, Biogen Idec, Britannia, Cynapsus, Depomed, Impax, Insightec, Intec, Kyowa Hakko, Lundbeck, Luye, NeuroDerm, Osmotica, Pfizer, ProS-trakan, Prothena, SynAgile, Teva, UCB Pharma, and USWorldMeds, and has received speaker honoraria from The International Parkinson's and Movement Disorders Society, Lundbeck, and USWorldMeds. He is compensated for services as Editor-in-Chief of *Clinical Neuropharmacology* and also serves without compensation on the editorial boards of *Journal of Neural Transmission*, *Translational Neurodegeneration*, and *Journal of Parkinson's Disease*. The Parkinson's Disease and Movement Disorders Program that Dr LeWitt directs has received clinical research grant support (for conducting clinical trials and other research) from AbbVie, Acorda, Adamas, Biotie, Kyowa Hakko, The Michael J. Fox Foundation for Parkinson's Research, the Parkinson Study Group, Pharma 2B, UCB, and USWorldMeds; Mika Leinonen is a biostatistician at 4Pharma AB, a contract research organization that provided compensated statistical consultation services to Civitas Therapeutics and also provides similar services to Acorda Therapeutics; Martin I. Freed was an employee of Civitas Therapeutics, the study sponsor that was responsible for the conduct of the study. This study was funded in part from a grant from the Michael J Fox Foundation for Parkinson's Research. Editorial assistance was provided by The Curry Rockefeller Group, LLC, which was funded by Acorda Therapeutics.

Funding

This study was supported in part by a grant from the Michael J Fox Foundation for Parkinson's Research. The study was funded by Civitas Therapeutics, now wholly owned by Acorda Therapeutics, Inc.

Supplemental data

Supplemental data for this article can be accessed at <http://dx.doi.org/10.1080/00207454.2016.1194274>.

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