Respiratory Medicine 182 (2021) 106396

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Original Research

# Natural history of lung function over one year in patients with Parkinson's disease

David A. Kaminsky [a,*], Donald G. Grosset [b], Deena M. Kegler-Ebo [c], Salvador Cangiamilla [c], Michael Klingler [c], Ping Zhao [c], Charles Oh [c]

[a] Larner College of Medicine, University of Vermont, Burlington, VT, USA
[b] Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK
[c] Acorda Therapeutics, Inc., Ardsley, NY, USA

ARTICLE INFO

*Keywords:*
Natural history
Parkinson's disease
Pulmonary function
Spirometry

ABSTRACT

*Background:* Little is known about decline in lung function in Parkinson's disease (PD). To assess these changes, we assessed the changes in lung function that occurred over 12 months in patients on standard PD therapy as part of the observational cohort of an open-label study of inhaled levodopa (CVT-301) in PD.

*Methods:* PD patients on stable oral PD therapy and no chronic respiratory disease had spirometry and diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) measured at 3, 6, 9, and 12 months.

*Results:* 106 patients (81.5%) in the observational cohort on no investigational therapy completed the study. Mean $FEV_1$ declined at 12 months from 2.88L at baseline with a mean change of −0.11L, greater than the −0.030–0.045L/year observed in healthy, non-smokers aged 60–70 years. FVC declined from 3.77L (mean change −0.19L); $FEV_1$/FVC ratio remained relatively constant. $DL_{CO}$ mean change was −0.48 mL/min/mmHg from a baseline of 24.24 mL/min/mmHg. This change in $DL_{CO}$, while not significant, was similar to that seen in non-smokers aged 60–70 years ($DL_{CO}$ -0.42–0.63 mL/min/mmHg/year). Decreases in alveolar volume (VA) and inspiratory vital capacity (IVC) rather than the transfer coefficient ($DL_{CO}$/VA) were observed.

*Conclusions:* PD patients had greater declines in $FEV_1$, and FVC, but not in $DL_{CO}$, compared to healthy non-smokers of similar age. Declines in $FEV_1$ and FVC with little change in $FEV_1$/FVC, and decline in VA and IVC with little change in $DL_{CO}$/VA, suggest these changes were due to decreases in lung volume and are compatible with progressive PD-associated respiratory muscle weakness.

*Trial registration:* ClinicalTrials.gov (NCT02352363 Registered January 26, 2015 [https://clinicaltrials.gov/ct2/show/NCT02352363]) and EudraCT (2014-003799-22).

## 1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by loss of dopaminergic neurons and reduction in striatal dopamine [1,2]. Patients experience motor symptoms (eg, tremor, rigidity, problems with balance and gait) as well as nonmotor symptoms (eg, depression, sleep disorders, cognitive impairment) [1,3]. PD has a prevalence greater than 1% at age 60 years and this increases to 5% after age 85 years [4]. Thus, a growing number of individuals will experience the adverse medical, psychosocial, and economic impacts of PD as the population ages [3]. Among these may be a loss of lung function.

Lung function abnormalities, including restriction, obstruction, and variability of flow-loop morphologies, are recognized in patients with PD and are thought to be due, in part, to respiratory and upper-airway muscle weakness [5–13]. Respiratory abnormalities are also related to the PD stage (especially pronounced in PD with autonomic failure) [5], motor fluctuations [6,10], or the occurrence of disabling dyskinesias that emerge in later stages of the disease [13–15]. Dyskinesia can lead to restrictive and dyskinetic ventilation, and disordered respiratory mechanics can lead to pulmonary infection, which is a major cause of mortality and morbidity in people with PD [13]. However, little is known about the natural history of decline in lung function in patients with idiopathic PD [9,10,13,16,17].

Even in healthy, nonsmoking adults, lung function decreases with age, as measured by forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), and $FEV_1$/FVC ratio [18,19]. According to a large

* Corresponding author. Vermont Lung Center, Larner College of Medicine, University of Vermont Burlington, VT, 05405, USA.
*E-mail address:* david.kaminsky@uvm.edu (D.A. Kaminsky).

https://doi.org/10.1016/j.rmed.2021.106396
Received 12 January 2021; Received in revised form 3 April 2021; Accepted 5 April 2021
Available online 16 April 2021

**Abbreviations**

| | |
|---|---|
| DLCO, | diffusing capacity of the lungs for carbon monoxide; |
| FEV1, | forced expiratory volume in 1 s; |
| FVC, | forced vital capacity; |
| IVC, | inspiratory vital capacity; |
| LD, | levodopa; |
| PD, | Parkinson's disease; |
| TLC, | total lung capacity; |
| VA, | alveolar volume |

multinational data set, $FEV_1$ is estimated to decrease by 0.030–0.045 L/year among healthy nonsmokers aged 60–70 years [19]. In an epidemiologic study, diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) declined by 0.42–0.63 mL/min/mmHg per year among men and women aged 60–70 years [20].

A 12-month, randomized, open-label, multicenter safety study of a levodopa (LD) inhalation powder (CVT-301, Inbrija™) [21] was conducted in people with PD. CVT-301-treated patients were compared to an observational cohort of patients on a standard PD medication regimen, and who did not receive CVT-301, to evaluate long-term pulmonary safety of the intervention. In addition to clinical efficacy of CVT-301, the results indicated no significant differences in pulmonary function for CVT-301-treated patients versus the observational cohort over 1 year, indicating pulmonary safety of CVT-301.

In this paper we present data obtained from pulmonary function testing in the observational cohort from the randomized, open-label 12-month study, as it provided an opportunity to evaluate changes in lung function over 1 year in a large set of patients with idiopathic PD treated with standard PD therapy, and not on investigational therapy. These data could then be compared to published data on the natural history of lung function decline over time in healthy people without PD.

## 2. Methods

### 2.1. Study population

Study participants were men and women diagnosed at age 30 or older with idiopathic PD, modified Hoehn and Yahr stage 1–3 in the ON state [22], ≥2 h average daily OFF time (excluding early-morning OFF time), on a stable dose of oral dopa decarboxylase inhibitor/LD regimen (≥3 daily doses with total LD dose ≤1600 mg/day), Unified Parkinson's Disease Rating Scale Part III [23] motor symptom improvement ≥25% from OFF to ON at screening, and Mini-Mental State Examination [24] score ≥25. Eligible patients had to be able to perform spirometry in the ON and OFF states and had to have $FEV_1$ ≥50% predicted value (from the NHANES [National Health and Nutrition Examination Survey] III predicted sets [18]) and $FEV_1$/FVC ratio >0.60 in the ON state at screening [25]. Candidates were excluded if they had dyskinesia that would interfere with study procedures or if they had any chronic respiratory disease (eg, asthma or chronic obstructive pulmonary disease) within the last 5 years. Current smokers were permitted to participate in the study provided they had no chronic respiratory disease within the last 5 years and they had $FEV_1$ ≥50% predicted and $FEV_1$/FVC >60% in the ON state at screening. A pulmonologist reviewed the spirometry tracings/morphology of any patient with an $FEV_1$ ≥50% to <60% of predicted or an $FEV_1$/FVC ratio that was >60% to <70% at screening to identify patients with possible abnormal spirometry outside of what would be expected with PD in order to determine study eligibility. Patients with an $FEV_1$/FVC ratio that was >60% to <70% at screening completed spirometry before and after the administration of a bronchodilator in a pulmonary function facility. The results of the bronchodilator challenge were reviewed by a pulmonologist before randomization. Any patient requiring pulmonary adjudication at screening was not randomly assigned until after full pulmonologist review. Patients in this multicenter study (NCT02352363) were recruited from 62 sites in Europe ($n = 50$), the United States ($n = 8$), and Israel ($n = 4$). The study was performed in accordance with the Declaration of Helsinki; all study sites received institutional review board approval and all patients gave written informed consent.

### 2.2. Study design and measures

The original study's primary objective was to assess pulmonary safety of CVT-301 at 12 months via spirometry and these results have been previously published [21]. This paper presents in detail the results from the observational cohort who received no CVT-301 but were on a standard PD medication regimen. Eligible patients with motor fluctuations were randomized in a 2:1 ratio via interactive web response system to receive CVT-301 84 mg or no treatment (observational cohort). Randomization was stratified by Hoehn and Yahr stage [22] (<2.5 versus ≥2.5 in the ON state) and screening spirometry ($FEV_1$ <60% of predicted or $FEV_1$/FVC ratio <0.70 versus $FEV_1$ ≥60% of predicted and $FEV_1$/FVC ratio ≥0.70). All spirometry values were measured according to standard guidelines of the American Thoracic Society and the European Respiratory Society [25]. All $DL_{CO}$ measurements were made in accordance with the single breath method of the American Thoracic Society and European Respiratory Society recommendations [26]. Quality assurance audits were conducted routinely throughout the study by an independent group. All patients in the observational cohort group were CVT-301–naïve.

All patients received optimized standard oral PD treatment (dopa decarboxylase inhibitor/LD, dopamine agonists, monoamine oxidase B inhibitors, or catechol-*O*-methyltransferase inhibitors) throughout the study and were not on investigational therapy. Patients' standard PD

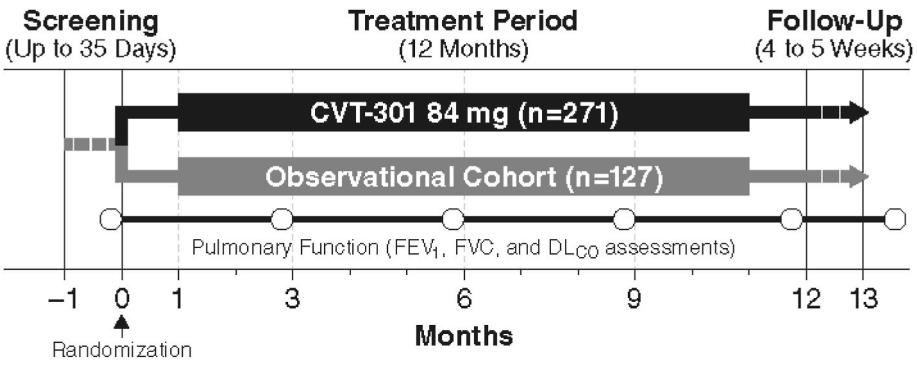


**Fig. 1.** Study design.
Abbreviations: $DL_{CO}$, diffusing capacity of the lungs for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.

**Table 1**
Demographics and characteristics for the observational cohort.

| Variable | Patients ($n = 127$) |
|---|---|
| Age, mean (range), years | 64.2 (38–79) |
| Sex, male, % | 61.4 |
| Race, white, % | 98.4 |
| BMI, mean (range), kg/m2 | 26.9 (16.2–45.9) |
| Region/Country, % | |
| Europe | 90.6 |
| Israel | 4.7 |
| United States | 4.7 |
| Smoking history,[a] % | |
| Never | 67.7 |
| Former | 26.0 |
| Current | 6.3 |
| Screening spirometry | 92.9 |
| $FEV_1$ ≥60% of predicted and $FEV_1$/FVC ≥0.70, % | |
| Modified Hoehn & Yahr scale, % | |
| <2.5 points | 47.2 |
| ≥2.5 points | 52.8 |
| Time since PD diagnosis, mean (SD), years | 9.7 (5.2) |
| Number of daily OFF periods, mean (SD) | 3.7 (1.0) |
| Daily OFF time, mean (SD), hours | 5.7 (2.1) |
| Duration of LD treatment, mean (SD), years | 7.3 (4.6) |
| Daily LD dose, mean (SD), mg | 874.1 (348.3) |
| Number of daily LD doses, mean (SD) | 5.2 (1.3) |

*BMI* body mass index, *$FEV_1$* forced expiratory volume in 1 s, *FVC* forced vital capacity, *LD* levodopa, *PD* Parkinson's disease, *SD* standard deviation.
[a] Mean 10.6 pack–years for those who were former and current smokers.

medication regimens could be altered as needed to manage their PD symptoms.

Study periods included a screening interval (up to 35 days), a treatment period of approximately 12 months, and a follow-up for pulmonary function 4–5 weeks after the last visit. Fig. 1 details the study design. During the treatment period, patients made study visits at baseline and 1, 3, 6, 9, and 12 months. Safety was assessed at a dedicated pulmonary function facility within 2 weeks before baseline; at 3, 6, 9, and 12 months; and at the final follow-up visit via measurement of $FEV_1$, FVC, $FEV_1$/FVC, and $DL_{CO}$ when patients were in the ON state. $DL_{CO}$ was further analyzed for underlying components of alveolar volume (VA) and inspiratory vital capacity (IVC).

Findings in the CVT-301 group have been previously reported [21]. The current assessment focuses on spirometry and $DL_{CO}$ values in the observational cohort only who were not on investigational therapy.

### 2.3. Statistical analysis

The safety population (for the observational cohort) included all observational cohort patients who attended at least 1 observation visit. Changes in spirometry and $DL_{CO}$ from baseline to study visit were evaluated within the observational cohort group. The point estimates and associated 95% confidence intervals were generated using a mixed model for repeated measures analysis, which included visit and the stratification variables (Hoehn and Yahr stage and screening spirometry) as fixed factors. The baseline value for each test was included as a covariate. For the subgroup analyses, descriptive statistics are presented. Calculations were performed with Statistical Analysis Software version 9.3 or higher (SAS Institute, Cary, NC). A 2-sided significance level of 0.05 was used without multiplicity adjustment.

## 3. Results

### 3.1. Patient characteristics

Of the 408 patients who were randomized in the original trial, 130 patients were assigned to the observational cohort. Of these, 127 were included in the safety population and 106 (81.5%) completed the study (one of the 106 patients did not have baseline assessment); 24 patients discontinued because of withdrawal of consent ($n = 21$) or other reasons ($n = 3$). Mean age was 64 years, 61% were male, and 98% were white; mean daily OFF time was 5.7 h and patients had received LD treatment for a mean of 7.3 years. Demographic and clinical characteristics for the observational cohort are listed in Table 1. Of note, the observational cohort did not differ in age, sex, or any clinical characteristics from the investigational cohort in the original study, except for being on a slightly higher mean (SD) dose of LD (874.1 (348.3) vs. 781.9 (357.7) mg/day.

### 3.2. Study measures

Mean $FEV_1$ declined in the observational cohort group from 2.88 L at baseline to 2.77 L by 1 year, for an absolute change of −0.12 L; LSM change (95% CI) of −0.11 L (−0.18 to −0.05 L); a 3.82% decrease from baseline (Table 2; Fig. 2). The mean change in FVC was similar, with a decline from 3.77 L at baseline to 3.64 L at 1 year (absolute change of −0.13 L; LSM change (95% CI) of −0.19 L (−0.28 to −0.11 L); 3.08% decrease from baseline). Of note, the change in percent predicted values for $FEV_1$ and FVC were also statistically significant. Given the similar declines in $FEV_1$ and FVC over 12 months, the $FEV_1$/FVC ratio remained relatively constant and within the normal range (77% at baseline; 76% at 1 year; LSM change [95% CI] of −0.73% [-2.01%–0.55%]; 0.52% decrease from baseline).

Table 3 shows the changes in $FEV_1$ by patient characteristics. Change in $FEV_1$ did not differ notably when classified by age (<65 years vs ≥ 65 years), sex, smoking history (current/former vs never), daily LD dose (<500 mg, 500–900 mg, and ≥900 mg), daily OFF time (<4.5 h vs ≥ 4.5 h), or number of concomitant PD medications (1–2 vs ≥ 3).

Mean $DL_{CO}$ decreased from 24.24 mL/min/mmHg at baseline to 23.47 mL/min/mmHg at 1 year, for an absolute change of −0.72 mL/min/mmHg (LSM change [95% CI] of −0.48 [-1.27 to 0.31]; 2.75% decline from baseline) (Table 4; Fig. 3). Of note, the change in the percent predicted value for $DL_{CO}$ was also not statistically significant (LSM change [95% CI] of −1.35 [-4.46 to 1.76]). Examination of the components of $DL_{CO}$ revealed that the decrease in $DL_{CO}$ was associated with statistically significant changes in volume measurements (VA and IVC) rather than the transfer coefficient as determined by $DL_{CO}$/VA (Table 4).

## 4. Discussion

Observation of a cohort of patients with PD taking standard therapy over 1 year revealed a faster rate of decline in lung function compared

**Table 2**
$FEV_1$ and FVC changes over 12 months.

| Parameter | Baseline[a] ($n = 103$) | 12 Months ($n = 103$) | Observed Change | LS Mean Estimated Change | 95% CI of LS Mean | % Change From Baseline |
|---|---|---|---|---|---|---|
| $FEV_1$, mean (SD), L | 2.88 (0.87) | 2.77 (0.84) | −0.12 (0.21) | −0.11 | −0.18, −0.05 | −3.82 (7.42) |
| $FEV_1$% predicted, mean (SD) | 98.4 (16.4) | 95.6 (16.8) | −2.8 (7.5) | −3.00 | −5.25, −0.76 | −2.7 (7.5) |
| FVC, mean (SD), L | 3.77 (1.07) | 3.64 (1.07) | −0.13 (0.29) | −0.19 | −0.28, −0.11 | −3.08 (8.36) |
| FVC % predicted, mean (SD) | 97.0 (15.4) | 94.5 (15.4) | −2.5 (7.8) | −4.01 | −6.14, −1.89 | −2.2 (8.5) |
| $FEV_1$/FVC %, mean (SD) | 76.60 (6.86) | 76.06 (6.40) | −0.54 (4.01) | −0.73 | −2.01, 0.55 | −0.52 (5.21) |

*$FEV_1$* forced expiratory volume in 1 s, *FVC* forced vital capacity, *LS* least squares, *CI* confidence interval.
[a] Based on 103 subjects who had data at 12 months.

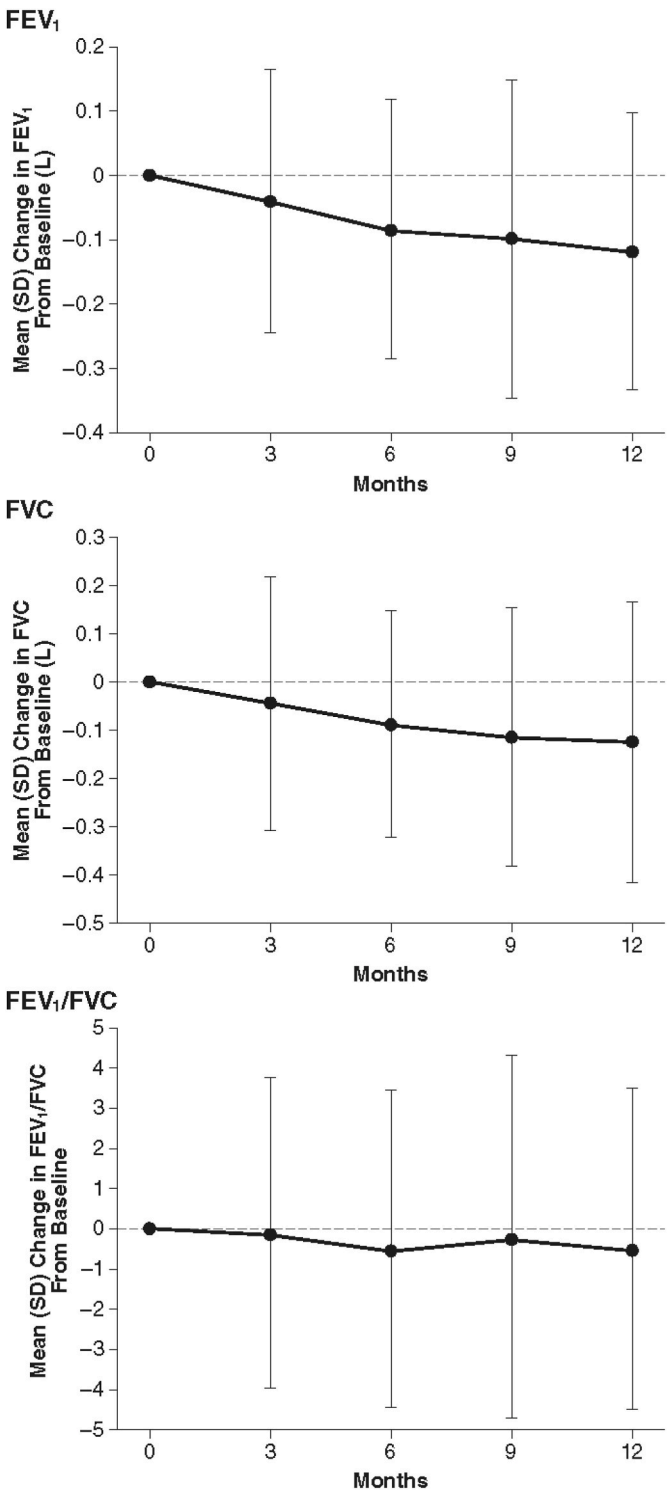


**Fig. 2.** Change in $FEV_1$, FVC, and $FEV_1$/FVC over 12 months.
Abbreviations: $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation.

with studies defining lung function in healthy subjects of similar age. Specifically, the observational cohort (mean age 64 years) showed an LSM decline in $FEV_1$ of 0.11 L over 1 year, approximately 3 times larger than the estimated rate of decline (0.030–0.045 L/year) in healthy nonsmoking individuals aged 60–70 years [19]; FVC decreased to a similar degree, at 0.19 L over 1 year. The decrease in $FEV_1$ also exceeds the commonly accepted minimal clinically important difference of 0.100 L suggested in treatment trials of patients with chronic obstructive

**Table 3**
$FEV_1$ change from baseline by patient characteristics ($N = 103$).

| Patient Characteristic | *n* | $FEV_1$ Change, mean (SD) |
|---|---|---|
| Age, years | | |
| <65 | 47 | −0.16 (0.24) |
| ≥65 | 56 | −0.08 (0.18) |
| Baseline ATS compliance | | |
| No | 38 | −0.16 (0.26) |
| Yes | 65 | −0.09 (0.18) |
| Dyskinesia | | |
| No | 62 | −0.13 (0.21) |
| Yes | 41 | −0.10 (0.22) |
| Sex | | |
| Female | 38 | −0.09 (0.21) |
| Male | 65 | −0.13 (0.22) |
| H&Y score | | |
| <2.5 | 52 | −0.12 (0.19) |
| ≥2.5 | 51 | −0.12 (0.23) |
| Daily LD dose | | |
| <500 mg/day | 12 | −0.21 (0.18) |
| 500–900 mg/day | 45 | −0.10 (0.18) |
| ≥900 mg/day | 46 | −0.11 (0.25) |
| Duration of LD treatment | | |
| <78 months | 49 | −0.10 (0.20) |
| ≥78 months | 54 | −0.13 (0.23) |
| Average daily OFF time | | |
| <4.5 h | 28 | −0.09 (0.23) |
| ≥4.5 h | 75 | −0.13 (0.21) |
| Number of PD concomitant medications | | |
| 1 | 7 | −0.06 (0.13) |
| 2 | 33 | −0.15 (0.25) |
| ≥3 | 63 | −0.11 (0.20) |
| Smoking history | | |
| Current | 6 | −0.13 (0.32) |
| Former | 25 | −0.11 (0.26) |
| Never | 72 | −0.12 (0.19) |

*ATS*, American Thoracic Society, *$FEV_1$* forced expiratory volume in 1 s, *H&Y* Hoehn and Yahr rating scale, *LD* levodopa, *PD* Parkinson's disease, *SD* standard deviation.

pulmonary disease [27]. However, the decline in $DL_{CO}$ of 0.48 mL/min/mmHg over 1 year was similar to the estimated decline (0.42–0.63 mL/min/mmHg) that occurs in healthy nonsmokers aged 60–70 years [20]. Both the changes in absolute value and the change in percent predicted were not statistically significant. Also, the absolute change did not reach the minimal clinically important difference of 1.1 mmHg/ml/min established in patients with chronic obstructive pulmonary disease [28]. These results indicate that lung function as measured by spirometry is lost at an accelerated rate in patients with PD at this stage of disease. Although the mechanism for this decline is unclear, our data suggest that the mechanism may be related to reduced muscle function.

Respiratory dysfunction in PD can derive from peripheral (eg, motor) and central mechanisms [12]. In our study, the decline in $FEV_1$ and FVC with little change in $FEV_1$/FVC over the 1-year study period suggests a decrease in lung volume rather than development or worsening of airway obstruction [29,30]. Similarly, although the $DL_{CO}$ did not change significantly, the decline in $DL_{CO}$ components of VA and IVC with little change in $DL_{CO}$/VA over 1 year suggests a decrease in lung volume rather than an intrinsic pulmonary parenchymal process that could lead to a reduction in gas exchange [30]. Unfortunately, spirometry cannot be used to measure lung volume directly, so a decrease in volume can only be inferred; direct measurement of lung volume by body plethysmography or gas dilution would be necessary to characterize the pattern of lung disease [29,30]. However, VA is a close surrogate for lung volume (or total lung capacity, TLC) when $FEV_1$/FVC is normal [31], as it is here. Therefore, since VA declined significantly, we can assume the same occurred for TLC, and this would be reflected in the decline in FVC and IVC as well.

Worsening of VA, IVC, $FEV_1$, and FVC, along with unchanged $DL_{CO}$, $DL_{CO}$/VA and $FEV_1$/FVC, suggests potential development of a restrictive

**Table 4**
$DL_{CO}$ changes over 12 months.

| Parameter | Baseline ($n$ = 95) | 12 Months ($n$ = 95) | Observed Change ($n$ = 95) | LS Mean Estimated Change | 95% CI of LS Mean | % Change From Baseline |
|---|---|---|---|---|---|---|
| $DL_{CO}$, mean (SD), mL/min/mmHg | 24.24 (7.10) | 23.47 (7.08) | −0.72 (2.49) | −0.48 | −1.27, 0.31 | −2.75 (10.24) |
| $DL_{CO}$ % predicted, mean (SD) | 97.7 (20.1) | 95.2 (20.6) | −2.3 (9.8) | −1.35 | −4.46, 1.76 | −2.0 (10.3) |
| VA, mean (SD), L | 5.50 (1.32) | 5.37 (1.31) | −0.11 (0.41) | −0.15 | −0.27, −0.03 | −1.79 (8.01) |
| IVC, mean (SD), L | 3.71 (0.98) | 3.61 (0.97) | −0.08 (0.30) | −0.14 | −0.23, −0.05 | −2.10 (8.60) |
| $DL_{CO}$/VA, mean (SD), mL/min/mmHg/L | 4.45 (0.88) | 4.39 (0.81) | −0.06 (0.61) | −0.07 | −0.23, 0.10 | −0.39 (12.99) |

*$DL_{CO}$* diffusing capacity of the lung for carbon monoxide, *IVC* inspiratory vital capacity, *LS* least squares, *CI* confidence interval, *SD* standard deviation, *VA* alveolar volume.

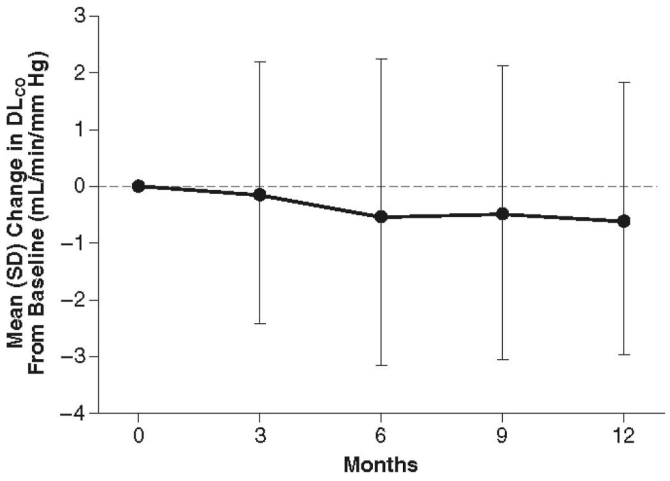


**Fig. 3.** Change in $DL_{CO}$ over 12 months.
Abbreviations: $DL_{CO}$, diffusing capacity of the lungs for carbon monoxide; SD, standard deviation.

pattern most likely due to dysfunction of respiratory muscles, which is particularly evident in the OFF versus the ON state [6,30]. The decline in pulmonary function was not explained by any of the subgroup analyses of the observational cohort, including OFF time, stage of PD, LD dose, or number of concomitant medications, and also smoking, where the $FEV_1$ changes from baseline for the 6 patients who were current smokers and the 25 who were former smokers were not substantively different from the 72 non-smokers.

Studies of the natural history of PD are few and have not provided definitive data because of diagnostic uncertainty, disease heterogeneity, differences in study cohorts (eg, age, duration of PD, treatment regimens), and underlying comorbidities [3]. Natural-history studies of pulmonary function in PD have also been relatively small, with short follow-up duration and conflicting results due to differences in patient ages, diagnostic definitions, disease severity, prescribed medications, pulmonary function testing methodology, and outcome measures used [16,17]. Lung function has obvious importance for its impact on respiration as well as speech, swallowing, sleep disturbance, exercise tolerance, and infection risk [17]. Pneumonia is the leading cause of death in patients with PD [3,16]. While we believe our results are best explained by progressive muscle weakness, abnormalities of lung function in patients with PD can occur independently of mechanical factors such as respiratory muscle strength [12,17]. The predominant pattern of abnormality in PD (obstructive, restrictive, mixed, or normal) as well as the role of respiratory muscle weakness have not yet been established [16,17].

Overall, we hypothesize that the accelerated rate of decline in pulmonary function in patients with PD may be due to a decline in lung volume, which we presume is secondary to progressive respiratory muscle weakness associated with PD. In order to investigate this hypothesis respiratory muscle strength would have had to be measured and this was not done. Further study of pulmonary dysfunction in PD is warranted to clarify prevalence, phenotypes, prognostic implications, and management, particularly as the prevalence of PD continues to increase as the population ages [3,4,16,17]. Of note, respiratory muscle training is beneficial to strengthen the respiratory muscles in these patients [32], so this might be a strategy to help prevent accelerated loss of lung function in patients with PD.

The limitations of this study include that it was a retrospective, observational study only, with multiple centers with the potential for variable measurement validity, although this was mitigated by direct oversight for quality; and employed comparison to historical healthy control data only.

## 5. Conclusions

In an observational cohort of patients on standard therapy for PD, there was an accelerated rate of pulmonary function decline over 1 year compared with data from studies defining lung function in healthy subjects of similar age. Results showing declines in $FEV_1$ and FVC with little change in $FEV_1$/FVC suggest a decrease in lung volume rather than development or worsening of airway obstruction. In addition, the decline in VA and IVC with little change in $DL_{CO}$ or $DL_{CO}$/VA suggests a decrease in lung volume rather than an intrinsic pulmonary parenchymal process that could lead to a reduction in gas exchange. In turn, the deterioration in pulmonary function is presumed to be due to progressive respiratory muscle weakness associated with PD, although further study is necessary to support this mechanism.

## Statement of ethics

The study was approved by independent ethics committees for each institution. All patients provided written informed consent prior to study start.

## Funding sources

This study was supported by Acorda Therapeutics. The sponsors provided data and were involved in the writing, reviewing and final approval of the submitted manuscript. Editorial assistance was provided by The Curry Rockefeller Group, LLC. Acorda funded this writing and editorial support.

## CRediT authorship contribution statement

**David A. Kaminsky:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Donald G. Grosset:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Deena**

**M. Kegler-Ebo:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Salvador Cangiamilla:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Michael Klingler:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Ping Zhao:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript. **Charles Oh:** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects, contributed substantially to the study design, Formal analysis, and interpretation, and the writing of the manuscript.

## Declaration of competing interest

DAK is Data Safety and Monitoring Board member for the clinical trials of Inbrija (CVT-301) sponsored by Acorda Therapeutics, Inc; faculty consultant for Cardiorespiratory Diagnostics seminar sponsored by MGC, Inc.

DGG received compensation for consulting services to Acorda Therapeutics, Inc. and honoraria from Bial, UCB Pharma, and GE Healthcare.

DMKE, and PZ are employees and own stock in Acorda Therapeutics, Inc.

SC, MK, and CO were employees and stockholders of Acorda Therapeutics, Inc. at the time of the study.

## Acknowledgements

Editorial assistance was provided by Laura J. Ninger, ELS, and Robin Smith, PhD, of the Curry Rockefeller Group, LLC, Tarrytown, NY, which was funded by Acorda Therapeutics, Inc.

## References

[1] Parkinson's Foundation, What is Parkinson's? [Available from: http://parkinson.org/understanding-parkinsons/what-is-parkinsons.
[2] A.H.V. Schapira, M. Emre, P. Jenner, W. Poewe, Levodopa in the treatment of Parkinson's disease, Eur. J. Neurol. 16 (9) (2009) 982–989.
[3] W. Poewe, The natural history of Parkinson's disease, J. Neurol. 253 (suppl 7) (2006) VII2–6.
[4] A. Reeve, E. Simcox, D. Turnbull, Ageing and Parkinson's disease: why is advancing age the biggest risk factor? Ageing Res. Rev. 14 (2014) 19–30.
[5] L.K. Brown, Respiratory dysfunction in Parkinson's disease, Clin. Chest Med. 15 (4) (1994) 715–727.
[6] M.F. De Pandis, A. Starace, F. Stefanelli, P. Marruzzo, I. Meoli, G. De Simone, et al., Modification of respiratory function parameters in patients with severe Parkinson's disease, Neurol. Sci. 23 (suppl 2) (2002) S69–S70.
[7] M.I. Freed, N.B. Hampson, T. DeFeo-Fraulini, A. Gentili, Spirometric abnormalities in Parkinson's disease (PD) with motor fluctuations: a prospective, longitudinal study [abstract], Mov. Disord. 29 (Suppl 1) (2014) S378.
[8] L.U. Guedes, J.M. Rodrigues, A.A. Fernandes, F.E. Cardoso, V.F. Parreira, Respiratory changes in Parkinson's disease may be unrelated to dopaminergic dysfunction, Arq Neuropsiquiatr 70 (11) (2012) 847–851.
[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.K. Pal, T.N. Sathyaprabha, P. Tuhina, K. Thennarasu, Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa, Mov. Disord. 22 (3) (2007) 420–424.
[11] M. Sabate, I. Gonzalez, F. Ruperez, M. Rodriguez, Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease, J. Neurol. Sci. 138 (1–2) (1996) 114–119.
[12] L.M. Seccombe, H.L. Giddings, P.G. Rogers, A.J. Corbett, M.W. Hayes, M.J. Peters, et al., Abnormal ventilatory control in Parkinson's disease–further evidence for non-motor dysfunction, Respir. Physiol. Neurobiol. 179 (2–3) (2011) 300–304.
[13] H. Shill, M. Stacy, Respiratory function in Parkinson's disease, Clin. Neurosci. 5 (2) (1998) 131–135.
[14] J.J. Ferreira, R. Katzenschlager, B.R. Bloem, U. Bonuccelli, D. Burn, G. Deuschl, et al., 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.
[15] J. Jankovic, Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations, Mov. Disord. 20 (S11) (2005) S11–S16.
[16] G. Baille, A.M. De Jesus, T. Perez, D. Devos, K. Dujardin, C.M. Charley, et al., Ventilatory dysfunction in Parkinson's disease, J. Parkinsons Dis. 6 (3) (2016) 463–471.
[17] A. O'Callaghan, R. Walker, A review of pulmonary function in Parkinson's disease, J. Park. Restless Legs Syndr. 8 (2018) 13–23.
[18] J.L. Hankinson, J.R. Odencrantz, K.B. Fedan, Spirometric reference values from a sample of the general U.S. population, Am. J. Respir. Crit. Care Med. 159 (1) (1999) 179–187.
[19] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, et al., 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.
[20] D.L. Sherrill, P.L. Enright, W.T. Kaltenborn, M.D. Lebowitz, Predictors of longitudinal change in diffusing capacity over 8 years, Am. J. Respir. Crit. Care Med. 160 (6) (1999) 1883–1887.
[21] D.G. Grosset, R. Dhall, T. Gurevich, J. Kassubek, W.H. Poewe, O. Rascol, et al., Inhaled levodopa in Parkinson's disease patients with OFF periods: a randomized 12-month pulmonary safety study, Park. Relat. Disord. 71 (2020) 4–10.
[22] C.G. Goetz, W. Poewe, O. Rascol, C. Sampaio, G.T. Stebbins, C. Counsell, et al., Movement disorder society task force report on the Hoehn and Yahr staging scale: status and recommendations, Mov. Disord. 19 (9) (2004) 1020–1028.
[23] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, The unified Parkinson's disease rating scale (UPDRS): status and recommendations, Mov. Disord. 18 (7) (2003) 738–750.
[24] 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.
[25] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, et al., Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005) 319–338.
[26] N. Macintyre, R.O. Crapo, G. Viegi, D.C. Johnson, C.P. van der Grinten, V. Brusasco, et al., Standardisation of the single-breath determination of carbon monoxide uptake in the lung, Eur. Respir. J. 26 (4) (2005) 720–735.
[27] 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.
[28] 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.
[29] K. Schultz, L.C. D'Aquino, M.R. Soares, A. Gimenez, CAdC. Pereira, Lung volumes and airway resistance in patients with a possible restrictive pattern on spirometry, J. Bras. Pneumol. 42 (5) (2016) 341–347.
[30] F. Al-Ashkar, R. Mehra, P.J. Mazzone, Interpreting pulmonary function tests: recognize the pattern, and the diagnosis will follow, Cleve. Clin. J. Med. 70 (10) (2003) 866, 8, 71-3, passim.
[31] C.M. Roberts, K.D. MacRae, W.A. Seed, Multi-breath and single breath helium dilution lung volumes as a test of airway obstruction, Eur. Respir. J. 3 (5) (1990) 515–520.
[32] V.A. van de Wetering-van Dongen, J.G. Kalf, P.J. van der Wees, B.R. Bloem, M. J. Nijkrake, The effects of respiratory training in Parkinson's disease: a systematic review, J. Parkinsons Dis. 10 (4) (2020) 1315–1333.