

## A Randomized Trial of Inhaled Levodopa (CVT-301) for Motor Fluctuations in Parkinson's Disease

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**ABSTRACT: Background:** Although levodopa is the most effective oral PD therapy, many patients experience motor fluctuations, including sudden loss of dose effect and delayed benefit. CVT-301 is a levodopa inhalation powder with the potential for rapid onset of action. The objective of this study was to evaluate CVT-301 self-administered by PD patients to relieve OFF episodes.

**Methods:** PD patients with  $\geq 2$  hours per day of OFF time despite oral levodopa  $\geq 4$  times per day were randomized to CVT-301 or placebo for 4 weeks, to be used up to 3 times per day for OFF episodes. After 2 weeks, the study-drug dose was escalated from 35 to 50 mg. The primary end point was mean change in UPDRS Part III score from a predose OFF state to the average of postdose scores obtained at 10, 20, 30, and

60 minutes, as assessed in-clinic at the end of week 4. Home diaries were recorded.

**Results:** Eighty-six patients used the study drug at an average frequency of 2.1 times per day for CVT-301 and for placebo. At 4 weeks, least-squares mean change in UPDRS Part III score favored CVT-301 by 7.0 points ( $P < 0.001$ ). A treatment effect was evident at 10 minutes. At 4 weeks, least-squares mean OFF-time change from baseline favored CVT-301 by 0.9 hours per day ( $P = 0.045$ ). The most frequently reported adverse events in the CVT-301 group were dizziness, cough, and nausea, each in 7% (3 of 43 patients).

**Conclusions:** CVT-301 self-administered during OFF episodes provided rapid improvement of motor function, and daily OFF time was significantly reduced at the higher dose. CVT-301 was generally safe and well-tolerated.

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Levodopa (LD) administered in combination with a dopa-decarboxylase inhibitor (DDI; carbidopa or benserazide) is the most effective oral treatment for the motor features of Parkinson's disease (PD).<sup>1</sup> As PD progresses, however, many patients gradually lose a predictable and sustained response to each LD dose.<sup>2-8</sup> Motor fluctuations manifested as OFF time affect an estimated 40% of LD-treated PD patients after 4 to 6 years of LD use, increasing to an estimated 70% after 9 years,<sup>3</sup> and can have a major impact on a patient's function, safety, and quality of life.<sup>9</sup> Irregular intestinal absorption of oral LD contributes to delayed or unpredictable LD benefit.<sup>10,11</sup> Strategies including shorter LD dosing interval, adjunctive drugs, and sustained-release formulations of oral LD have not resolved these problems.<sup>12</sup>

CVT-301<sup>13,14</sup> is a novel LD inhalation powder formulated for pulmonary absorption and administered using a passive, breath-actuated delivery system<sup>15</sup> that has undergone extensive clinical testing for the delivery of inhaled agents ranging from small molecules<sup>16</sup> to proteins.<sup>17,18</sup> In a phase 2a dose-finding, CVT-301 study with a crossover design, 24 PD patients received single in-clinic doses of standard oral LD and each of 3 inhaled double-blind treatments: placebo, CVT-301 as a 25-mg fine-particle dose (FPD), and CVT-301 as a 50-mg FPD.<sup>19</sup> In each instance, the FPD is the quantity of LD estimated to reach the lungs. Each treatment was administered during an OFF episode occurring 4 to 5 hours after the patient's first daily oral levodopa dose (plus a DDI) with or without other PD medications. After the CVT-301 inhalations, plasma LD concentrations were found to increase more rapidly and with less variability than was observed in the same patients after oral LD dosing. Improved motor function, as assessed by timed finger-tapping<sup>20</sup> and by Part III motor-examination scores on the Unified Parkinson's Disease Rating Scale (UPDRS),<sup>21</sup> was recognized at the first assessment point, 5 minutes and 15 minutes, respectively. The improvements persisted through assessments at 90 minutes. After CVT-301 inhalations, the only adverse event reported by more than 1 patient was cough, in 6 patients (25%). No serious or severe adverse events were reported, and patients exhibited no decline in pulmonary function test results. The objective of the current phase 2b study was to evaluate the efficacy and safety of CVT-301 self-administered by PD patients in a clinical setting and at home during OFF episodes.

## Methods

This was a 4-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group dose-escalation trial. The trial included a screening period lasting 2 to 4 weeks, a treatment period lasting 4 weeks, and a follow-up safety visit 1 week after the end of treatment. The trial was conducted at 13 sites in the United States, 3 in Italy, 2 in Serbia, and 2 in the United Kingdom and was registered with ClinicalTrials.gov (identifier: NCT01777555).

### Study Participants

All patients were required to be 30 to 80 years of age and have typical clinical features of PD. Each patient also had a modified Hoehn and Yahr (H&Y) rating<sup>22</sup> of stages 1-3 in the ON state and recognizable, predictable OFF episodes totaling  $\geq 2$  hours per day (excluding early-morning OFF time). Each patient's UPDRS Part III scores were required to show a  $\geq 25\%$  decrease (improvement) from OFF to ON in response to the patient's usual morning dose of LD. In the ON state, the patient's forced expiratory volume during the first second of expiration (FEV<sub>1</sub>) was required to be  $>60\%$  of the value predicted by the patient's age, sex, height, and race,<sup>23</sup> and the ratio of FEV<sub>1</sub> to forced vital capacity was required to be  $\geq 75\%$ . The patient's PD medications were required to include oral LD taken at least 4 times daily in a regimen stable for at least 2 weeks prior to screening. PD treatment could also include stable dosages of other marketed oral PD medications (dopaminergic agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, and anticholinergics). Exclusion criteria included a history of chronic respiratory disease within the preceding 5 years and a Mini-Mental State Examination<sup>24</sup> score  $< 25$ .

### Study Design

As part of their screening, all patients were taught how to prepare and use the inhaler system, using sham drug capsules. The training took place during an ON state and was repeated during the subsequent OFF state and also at a second screening visit. By an interactive web response system, enrolled patients were randomized in a 1:1 ratio to self-administer inhaled CVT-301 or placebo for 4 weeks to treat OFF episodes on an as-needed basis up to 3 times/day. The

randomization was stratified by baseline PD severity, as measured by H&Y stage at screening ( $<2.5$  vs  $\geq 2.5$ ). During weeks 1 and 2, patients used a 35-mg LD FPD or indistinguishable placebo (the content of 2 capsules). During weeks 3 and 4, patients used a 50-mg LD FPD or placebo (the content of 3 capsules). Placebo was supplied as an inhalation-grade lactose monohydrate designed to produce a sensation of dose administration and approximate the upper respiratory powder-load deposition of the active drug but not enter the lungs. Throughout the study, each patient's usual regimen of PD medications was held constant, and apomorphine was not permitted.

### Efficacy Assessments

At the beginning of treatment and at the end of weeks 1, 2, and 4, each patient prepared and self-administered an in-clinic study-drug dose. At the end of weeks 2 and 4, the dose was 3 capsules (beginning and ending the patient's use of this dose level). At the end of weeks 1, 2, and 4, the preparation and self-dosing occurred in an investigator-confirmed OFF state.

UPDRS Part III scores were obtained at screening and at the end of weeks 1, 2, and 4. During each of the latter 3 visits, scores were obtained for the predose OFF state and the 10-, 20-, 30-, and 60-minute post-dose by an investigator blinded to treatment group. In addition, each patient was rated subjectively as achieving or not achieving an ON state during the 60-minute observation period. At the end of weeks 2 and 4, patients used the Patient Global Impression of Change (PGI-C) Scale<sup>25</sup> to respond to the question "How has the addition of study drug changed your Parkinson's disease?" The scale offers 7 ratings, from "much improved" to "much worse." For the 3 days preceding every visit, patients maintained a home PD diary<sup>26</sup> in which they recorded their predominant clinical state during each half-hour of the waking day as OFF, ON with no dyskinesia, ON with nontroublesome dyskinesia, or ON with troublesome dyskinesia. Ease of inhaler-system use was not formally assessed. However, study sites recorded the amount of time a patient needed for each in-clinic use, and during week 2, a protocol-specified telephone contact elicited patients' concerns.

### Statistical Methods

The study's predefined primary efficacy end point was each treatment group's least-squares (LS) mean change from predose UPDRS Part III score to the average postdose score (across the 10- to 60-minute assessment times) at the end of week 4. The end point was tested for a significant difference between CVT-301 50 mg and placebo (defined as  $P < 0.05$ ), using a mixed model for repeated measurements (MMRM) with baseline H&Y stage ( $<2.5$  vs  $\geq 2.5$ ), country,

treatment group, visit, and treatment-by-visit interaction as fixed factors and baseline UPDRS Part III OFF-state score as a covariate. UPDRS Part III findings at other visits were tested in the same way, as predefined secondary end points. The proportions of patients achieving predefined UPDRS Part III score reductions of at least 3, 6, and 11 points at each post-dose assessment point were evaluated descriptively. The proportion of patients rated as achieving an ON state at a given visit was also assessed descriptively. PGI-C responses were collapsed into 3 categories: "improved," "no change," and "worse." The resulting response distributions were assessed descriptively as a predefined exploratory efficacy outcome. All diary data were normalized to a 16-hour waking day by extrapolation of valid entries after exclusion of time asleep. For each clinical-state category, LS mean changes from baseline values (obtained during screening) were analyzed by an MMRM as predefined secondary end points.

### Sample-Size Calculation

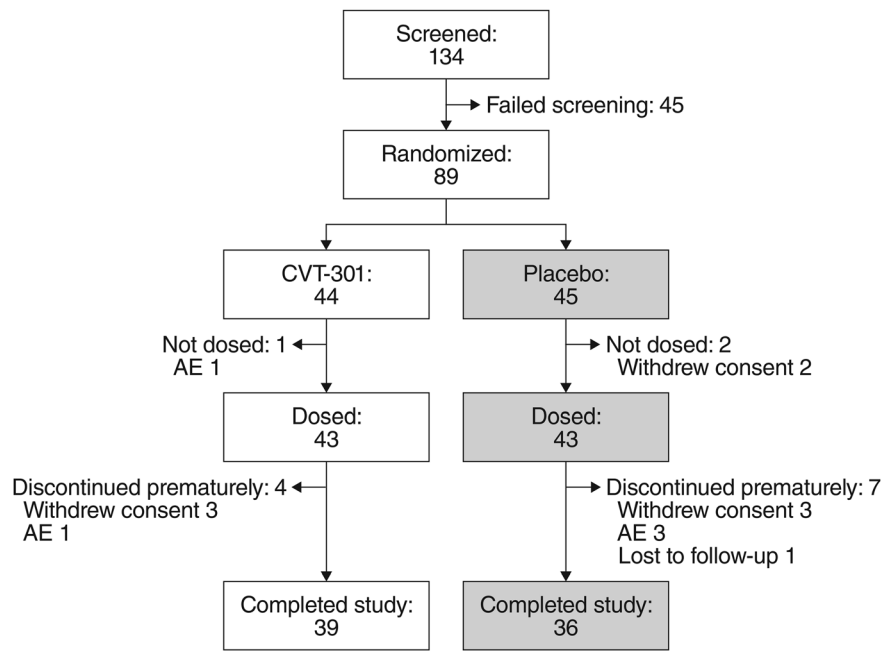
Twenty-nine patients per treatment group was estimated to provide a power of 90% to detect a group difference of 5.3 points in the primary end point (within the range considered a moderate clinically important difference [CID]<sup>27</sup>), assuming a standard deviation (SD) of 6.1 points (based on previous studies and historical data). To overcome a predicted dropout rate of ~30%, the total planned enrollment was 40 patients per group.

### Safety Assessments

Safety was assessed descriptively by measures including treatment-emergent adverse events (TEAEs), physical examination findings, clinical laboratory values, electrocardiography, and spirometry. All spirometry was performed by qualified, trained personnel using standardized equipment under guidelines specified by the Third National Health and Nutrition Examination Survey, the American Thoracic Society, and the European Respiratory Society.<sup>23,28</sup> At screening, spirometry included examinations in each patient's ON and OFF states during a single visit. At each visit during the treatment period, spirometry was performed on patient arrival. At the visits initiating the use of each study-drug dose level (ie, the beginning of week 1 and the end of week 2), spirometry was also performed immediately predose and 15, 30, and 60 minutes postdose.

### Ethical Conduct

The study was conducted in accordance with ethical principles originating in the Declaration of Helsinki, Good Clinical Practices, and local regulatory



**FIG. 1.** Patient disposition. AE, adverse event.

requirements. Before any study procedures, the study protocol, investigational drug brochure, and informed consent forms were approved by appropriately constituted independent ethics committees and institutional review boards, and patients provided written informed consent.

## Results

### Study Participants

Patient disposition is summarized in Figure 1. Of 134 patients screened at 20 sites, beginning in April 2013, 89 were enrolled and randomized. Among them, 86 patients (97%) used at least 1 dose of study drug (thereby comprising the study's modified intent-to-treat population), and 75 (87%) completed the study, the last in January 2014.

Average age  $\pm$  SD of study participants was  $62.4 \pm 8.7$  years, with PD diagnosed an average of  $9.4 \pm 3.9$  years previously. Their mean OFF time, as recorded in their PD diaries, was  $5.8 \pm 2.0$  hours per day, including early-morning OFF time. Their mean LD intake was  $770 \pm 306$  mg/day, divided into  $5.9 \pm 1.9$  daily doses. However, the mean LD intake was lower and MAO-B inhibitor use more common in the CVT-301 group than in the placebo group (Table 1).

### Study-Drug Exposure

Patients used the study drug on an average of  $24.3 \pm 6.7$  days in the CVT-301 group and  $24.4 \pm 7.7$  days in the placebo group over a total period averaging  $28.4 \pm 5.4$  days in the CVT-301 group and  $26.7 \pm 7.6$  days in the placebo group. The average dosing

frequency over the total period was  $2.1 \pm 0.6$  doses/day in the CVT-301 group and  $2.1 \pm 0.7$  doses/day in the placebo group.

### Ease of Inhaler Use

During in-clinic OFF episodes, patients completed 2-capsule self-dosing in a mean  $1.5 \pm 1.0$  minutes and 3-capsule self-dosing in a mean  $1.9 \pm 0.9$  minutes. Across all telephone contacts, 14% of the CVT-301 group (6 of 42 contacted patients) and 7% of the placebo group (3 of 41 contacted patients) had concerns about inhaler system use. The only complaint by more than 1 patient was difficulty puncturing capsules (by 2 CVT-301 users and 1 placebo user).

### Efficacy by UPDRS Part III Score

By in-clinic assessment, mean change from predose to average postdose UPDRS Part III score showed statistically significant dose-ordered improvement in motor function after CVT-301 inhalation during an OFF episode (Supplemental Figure A). For 35 mg, the LS mean change in UPDRS Part III score was -9.9 points at the end of week 1 compared with -5.3 points in patients taking placebo, a treatment effect of -4.6 points (95% confidence interval [CI], -7.9 to -1.3 points;  $P = 0.007$ ). One week later, the first dosing of 50 mg yielded an LS mean change of -10.2 points compared with -3.5 points for the placebo, a treatment effect of -6.6 points (95% CI, -9.8 to -3.4 points;  $P < 0.001$ ). At the end of week 4, the LS mean change was -10.0 points for 50 mg versus -3.1 points for the placebo, a treatment effect of -7.0 points (primary efficacy analysis; 95% CI, -10.3 to -3.6;  $P < 0.001$ ). In the 27 CVT-301-group and



**TABLE 1.** Patients' baseline characteristics (mITT population)

Variable	CVT-301 Group (n = 43)	Placebo Group (n = 43)	P Value CVT-301 vs Placebo <sup>a</sup>
Age (years), mean (SD)	62.0 (8.4)	62.7 (9.1)	0.721
Sex, n (%)			0.110 <sup>b</sup>
Male	25 (58)	32 (74)	
Female	18 (42)	11 (26)	
Race, n (%)			1.000 <sup>c</sup>
White	41 (95)	42 (98)	
Other	2 (5)	1 (2)	
Time since PD diagnosis (years), mean (SD)	9.0 (3.8)	9.8 (4.0)	0.377
Time since emergence of motor fluctuations, years, mean (SD)	4.7 (3.9)	3.9 (3.3)	0.304
UPDRS, Part III score, mean (SD)			
OFF	35.4 (12.0)	36.2 (12.1)	0.741
ON	16.2 (8.1)	18.9 (9.8)	0.170
OFF time, hours/day, <sup>d,e</sup> mean (SD)	5.7 (2.2)	5.8 (1.8)	0.860
OFF episodes, number/day, <sup>d,e</sup> mean (SD)	3.5 (1.1)	3.7 (1.0)	0.380
ON time, hours/day, <sup>d</sup> mean (SD)			
With no dyskinesia	8.2 (3.4)	8.3 (3.5)	0.940
With nontroublesome dyskinesia	1.7 (2.5)	1.6 (2.6)	0.926
With troublesome dyskinesia	0.4 (1.1)	0.3 (1.0)	0.726
Modified Hoehn & Yahr stage when ON, n (%)			0.825
<2.5	27 (63)	26 (61)	
≥2.5	16 (37)	17 (40)	
Duration of LD treatment (years), mean (SD)	7.6 (3.8)	7.9 (4.0) <sup>f</sup>	0.717
LD dosage, mg/day, mean (SD)	687 (276)	853 (315)	0.011
LD doses, number/day, mean (SD)	5.6 (1.4)	6.1 (2.2)	0.261
Other PD drug use, n (%)			
Dopaminergic agonists	31 (72)	26 (61)	0.254 <sup>b</sup>
MAO-B inhibitors	23 (54)	14 (33)	0.050 <sup>b</sup>
COMT inhibitors	17 (40)	17 (40)	1.000 <sup>b</sup>
Amantadine	16 (37)	13 (30)	0.494 <sup>b</sup>

<sup>a</sup>Unpaired *t* test, unless stated otherwise.

<sup>b</sup>Chi-square test.

<sup>c</sup>Fisher's exact test.

<sup>d</sup>Three-day averages.

<sup>e</sup>Including early-morning OFF time.

<sup>f</sup>n = 42.

COMT, catechol-*O*-methyltransferase; LD, levodopa; MAO-B, monoamine oxidase B; mITT, modified intent to treat; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

26 placebo-group patients with a baseline H&Y rating < 2.5, the treatment effect at the end of week 4 was -4.7 points (95% CI, -9.2 to -0.1 points; *P* = 0.044). In the 16 and 17 patients with a baseline H&Y rating ≥ 2.5, it was -10.2 points (95% CI, -15.7 to -4.6 points; *P* < 0.001).

Figure 2 charts the serial UPDRS Part III scores obtained at the end of weeks 1 and 4. By post hoc analyses using an MMRM model, onset of action at both CVT-301 dose levels was evident at 10 minutes (the first assessment time) and the mean improvement in motor scores remained significant versus placebo through the 60-minute final assessment. At 60 minutes, the week 4 treatment effect (50 mg vs placebo) exceeded the week 1 treatment effect (35 mg vs placebo) by 4.3 points (95% CI, 0.3 to 8.3 points; *P* = 0.343).

At the end of week 1, 74% of the CVT-301 group achieved a UPDRS Part III score reduction ≥ 6 points by 30 minutes compared with 53% of the placebo group. For a reduction ≥ 11 points, the proportion

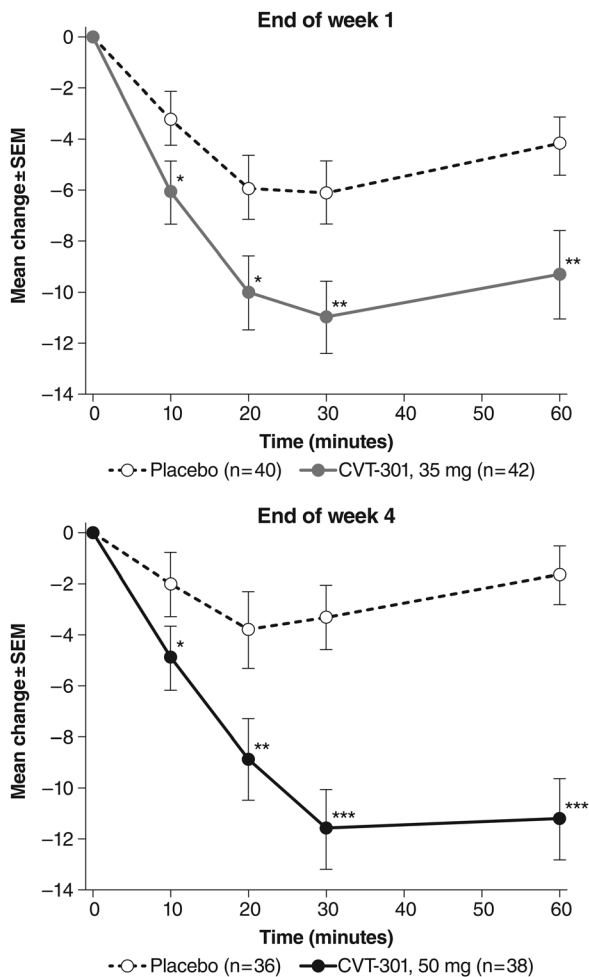
was 55% versus 28%. At the end of week 4, 79% of the CVT-301 group achieved a reduction ≥ 6 points by 30 minutes compared with 33% of the placebo group. For a reduction ≥ 11 points, the proportion was 58% versus 28%.

### Efficacy by Examiner Ratings

In the CVT-301 group, the proportion of patients achieving an ON state in an examiner's judgment increased from 67% (28 of 42 patients) in week 1 (35-mg FPD) to 74% (29 of 39) and 78% (29 of 37) in weeks 2 and 4, respectively (50-mg FPD). In the placebo group, the proportion was 45% (18 of 40) in week 1, 41% (16 of 39) in week 2, and 36% (13 of 36) in week 4.

### Efficacy by PGI-C Self-Ratings

At the end of week 2 (ie, the end of the 35-mg self-dosing period), 65% of the CVT-301 group and 44%



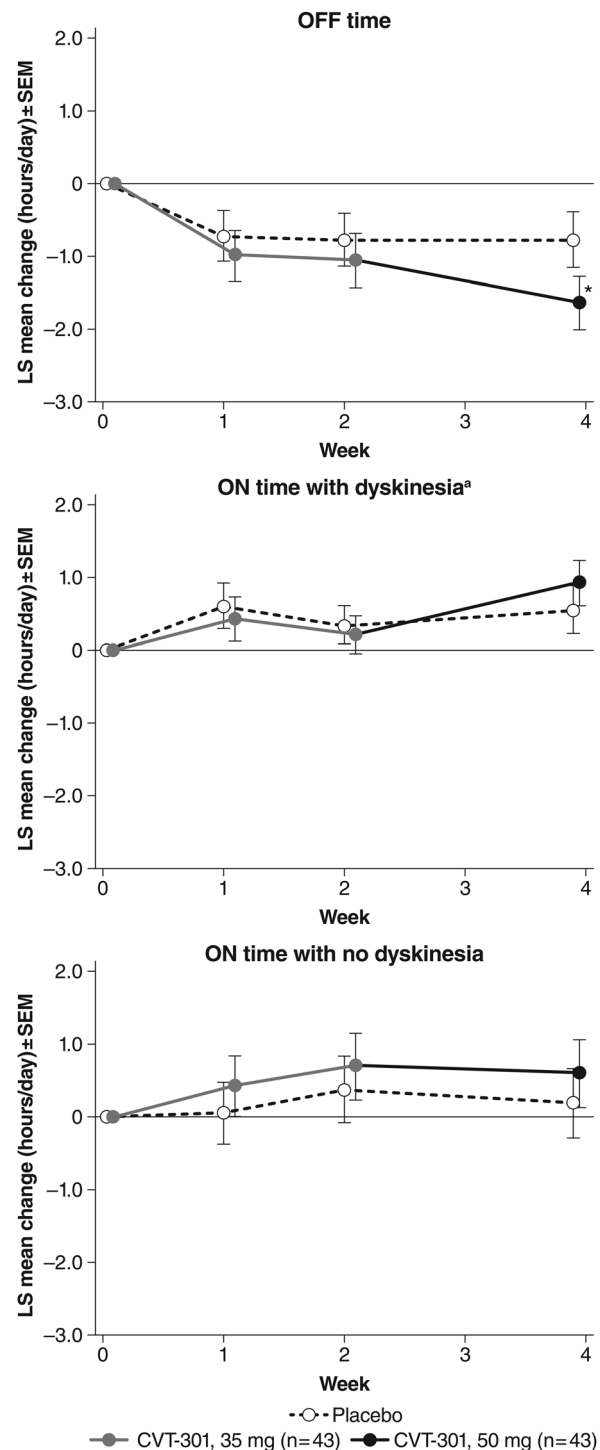
**FIG. 2.** Mean serial UPDRS Part III score change for 2 CVT-301 dose levels versus placebo (mITT population). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs placebo, MMRM. mITT, modified intent to treat; MMRM, mixed model for repeated measurements; SEM, standard error of the mean; UPDRS, Unified Parkinson's Disease Rating Scale.

of the placebo group rated their PD as improved, 28% and 51% rated it as unchanged, and 8% and 5% rated it as worse. At the end of week 4 (ie, the end of the 50-mg self-dosing period), 72% of the CVT-301 group and 46% of the placebo group rated their PD as improved, 18% and 54% rated it as unchanged, and 10% and 0% rated it as worse.

### Efficacy by Diary Data

Across all diary-entry categories, the only statistically significant difference between treatment groups was in OFF time (Fig. 3), which at the end of week 4 showed an LS mean decrease of 1.6 hours/day for CVT-301 dosed at 50 mg compared with 0.8 hours/day for placebo, a treatment effect of -0.9 hours/day (95% CI, -1.7 to 0.0 hours/day;  $P = 0.045$ ). For CVT-301 dosed at 35 mg, the LS mean OFF-time decrease at the end of week 2 was 1.1 hours/day compared with 0.8 hours/day for placebo, a treatment effect of -0.3 hours/day (95% CI, -1.1 to 0.6 hours/day;  $P = 0.498$ ). At both

doses, changes in ON time with troublesome or non-troublesome dyskinesia and in ON time with no dyskinesia were not significant (see Fig. 3).



**FIG. 3.** LS mean change in OFF time, in ON time with dyskinesia, and in ON time with no dyskinesia throughout the study, based on 3-day averages from PD diary entries (mITT population). \* $P < 0.05$  vs placebo, MMRM. <sup>a</sup>Troublesome or nontroublesome. LS, least squares; mITT, modified intent to treat; MMRM, mixed model for repeated measurements; PD, Parkinson's disease; SEM, standard error of the mean.

**TABLE 2.** Treatment-emergent adverse events (safety population)

TEAE Incidence, n (%)	CVT-301 Group			Placebo Group (n = 43)
	At any time (n = 43)	While Using 35 mg (n = 42)	While Using 50 mg (n = 42)	
<i>Summary</i>				
Any TEAE	20 (47)	17 (41)	9 (21)	14 (33)
Any study-drug-related TEAE	10 (23)	8 (19)	6 (14)	9 (21)
Any severe TEAE	0	0	0	2 (5)
Any serious TEAE	0	0	0	1 (2)
Any TEAE leading to study-drug dose adjustment	1 (2)	1 (2)	1 (2)	2 (5)
Any TEAE leading to study-drug discontinuation	2 (5)	1 (2)	1 (2)	3 (7)
Any TEAE leading to death	0	0	0	0
<i>By Preferred Term<sup>a</sup></i>				
Dizziness	3 (7)	3 (7)	0	2 (5)
Cough	3 (7)	2 (5)	1 (2)	1 (2)
Nausea	3 (7)	1 (2)	2 (5)	0
Headache	2 (5)	2 (5)	0	2 (5)
Edema peripheral	2 (5)	0	2 (5)	1 (2)
Anxiety	2 (5)	0	2 (5)	0
Sputum discolored	2 (5)	0	2 (5)	0

<sup>a</sup>Per Medical Dictionary for Regulatory Activities version 15.1. The list includes all TEAEs reported in more than 1 patient in either treatment group. TEAE, treatment-emergent adverse event.

### Safety

Twenty patients (47%) in the CVT-301 group and 14 patients (33%) in the placebo group reported TEAEs (Table 2). By preferred term, the TEAEs with an incidence  $\geq 5.0\%$  in the CVT-301 group were dizziness, cough, and nausea, each of which was reported in 3 patients (7%). As a TEAE, dyskinesia was reported in 1 patient (2%) in each treatment group. Two patients, both in the placebo group, experienced severe TEAEs: drop attack (also rated a serious TEAE) and dyskinesia.

One patient in the CVT-301 group and 2 in the placebo group experienced TEAEs that led to study-drug dose adjustment. In the CVT-301 group, the events were headache and nausea, at different times in the same patient; in the placebo group, the events were chest pain and dyskinesia, each in 1 patient. Two patients in the CVT-301 group and 3 in the placebo group experienced TEAEs leading to study-drug discontinuation. In the CVT-301 group, the events were painful respiration and sputum discoloration. The painful respiration occurred on treatment day 6 in a 67-year-old man whose medical history included congestive heart failure, 2 myocardial infarctions, hypertension, and anxiety. The event was rated as moderate and as resolving the same day. The sputum discoloration began on treatment day 20 in a 61-year-old man who exhibited cough 5 days earlier, followed by influenza symptoms. The event was rated as moderate and as resolving 6 days after CVT-301 discontinuation, at which time the patient's cough was ongoing. In the placebo group, the TEAEs leading to study-drug discontinuation were bradykinesia, chest pain, and wrist fracture. No deaths occurred during the study.

All other safety assessments identified no unexpected concerns. Among spirometry findings, characteristic PD-associated morphologies in flow-volume curves—that is, sawtoothing and a rounded, delayed expiratory peak<sup>29,30</sup>—were noted at similar frequencies across treatment groups. Mean values of all pulmonary function parameters were within normal ranges, showed no substantial difference between patients' ON and OFF states, and showed no evidence of longitudinal change in either treatment group.

### Discussion

In a population of PD patients experiencing motor fluctuations on orally administered LD, supplementary self-administration of CVT-301, an LD inhalation powder, provided rapid amelioration of OFF episodes. Serial UPDRS Part III scores showed a treatment effect at 10 minutes, the first assessment time. The treatment effect was maximal at 30 minutes and was sustained for  $\geq 60$  minutes. At 60 minutes, the effect was larger at the higher dose (see Fig. 2), implying a longer effect duration. Home-diary data showed a dose-ordered reduction of the daily duration of OFF time with statistical significance versus the placebo at the higher dose. At both dose levels, patients showed no significant increase in ON time with dyskinesia. Although patients were neither selected nor excluded based on their ability to use the drug inhaler system, patients were able to prepare and self-administer the treatment with relative ease in their OFF states.

As measured by UPDRS Part III scores, the average improvement in motor function was similar for both dose levels. However, the average difference from

placebo was numerically greater after the 50-mg dose, at least partly because of a decrease in placebo response in weeks 2 and 4 compared with week 1. In PD clinical research, a strong placebo response is typical and may reflect activation of residual nigrostriatal dopaminergic function by expectation of treatment benefit.<sup>31,32</sup> Thus, the observed decrease might represent treatment unmasking as the trial proceeded by cumulative experience with an inert intervention. The average improvement associated with active treatment—9.9 points after week 1, 10.2 points after week 2, and 10.0 points after week 4—greatly exceeded the reported minimum values for a clinically relevant change in Part III scores.<sup>27,33-36</sup> In analyses based on cross-sectional Part III data representing all PD stages,<sup>27</sup> 2.5 points has been judged to be a minimal CID, 5.2 to be a moderate CID, and 10.8 to be a large CID. In the present study, a majority of patients in the CVT-301 group achieved an 11-point change (55% in week 1 and 58% in week 4).

Throughout the 4 weeks of its use, CVT-301 was generally well tolerated at both dose levels. Among the TEAEs most frequently reported in the CVT-301 group, nausea, a symptom commonly associated with dopaminergic therapies in PD patients, caused only 1 patient to reduce the CVT-301 dose and no patient to withdraw from the study. Dizziness caused no CVT-301 dose reductions or discontinuations, and its incidence in the placebo group (5%) resembled that in the CVT-301 group (7%). Although dyskinesia is associated with long-term LD use,<sup>3</sup> TEAE incidence corroborated the study's diary data in showing no increase in dyskinesia occurrence. Dyskinesia is also associated with peaks in LD plasma level.<sup>37</sup> However, patients' self-treatment of their OFF episodes would presumably have occurred during troughs in the level. Because CVT-301 is an inhaled drug, cough was of special interest. In both treatment groups, all reported instances of cough were mild, none led to dose reduction or discontinuation, and no patient in either group reported dyspnea, wheezing, or bronchospasm.

The study may have been limited by requiring patients to restrict their study-drug self-administration to not more than 3 times daily despite having, on average, a reported baseline OFF-episode frequency of 3.6 per day (albeit including early-morning off time). Indeed, the baseline OFF-episode frequency ranged up to 7 per day, yet study-drug usage averaged only 2.1 times per day. Conceivably, patients may have held back on study-drug use each day to keep it available for potential severe episodes or times of need to be ON. Patients may also have refrained from using the study drug soon before their usual PD treatment. Although PGI-C self-ratings of PD improvement favored CVT-301, these ratings were global impressions following weeks of study-drug use, rather than

patients' impressions of benefit during specific OFF episodes. As a further limitation, the study assessed 35- and 50-mg dosing only as sequential treatments. Hence, the differences observed between them might reflect overall treatment duration rather than dose strength. The study did not assess the potential utility of CVT-301 for treating morning akinesia, which is common in patients with wearing-off responses to oral LD.

Among available PD pharmacotherapies, the dopaminergic agonist apomorphine offers the rapid action required to lessen OFF episodes.<sup>38</sup> In patients receiving repeated subcutaneous injections until their response resembled their usual levodopa response, a UPDRS Part III effect size of 23.8 points was achieved, and 1-month outpatient usage was reported to abort 95% of OFF episodes versus 23% for placebo.<sup>39</sup> Studies of randomized withdrawal<sup>40,41</sup> and long-term open-label self-treatment<sup>42,43</sup> were also positive. However, apomorphine is ineffective if taken orally, and subcutaneous injection often requires premedication with an antiemetic. Currently-marketed formulations also present safety and tolerability issues including nausea, vomiting, and development of subcutaneous nodules at injection sites.<sup>44</sup> Other forms of apomorphine have been or are in development.<sup>45-48</sup> ■

## Conclusions

OFF-episode reversal by a well-tolerated noninvasive intervention remains an important unmet clinical need. In the present study, inhalation of LD formulated as CVT-301 achieved rapid improvement of OFF states and reduced daily OFF time without an increase in dyskinesia or in severe or serious TEAEs. The study's findings support continued investigation of CVT-301 for rapid treatment of OFF episodes.

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