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Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease

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ABSTRACT

Background: CVT-301 (Inbrija) is a self-administered orally inhaled levodopa approved for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa/levodopa. Prior studies only evaluated CVT-301 after the first ON of the day.

Objective and methods: The objective of this study was to evaluate the safety and tolerability of CVT-301 for early morning OFF. Using a randomized, double-blind, 2-way crossover design, eligible patients in the morning OFF state (having not received PD medication overnight) received a single dose of CVT-301 84 mg or placebo on 2 dosing days, immediately after their first morning oral carbidopa/levodopa dose. Safety assessments included treatment-emergent adverse events, vital signs, and patient- and examiner-reported dyskinesia. An exploratory efficacy assessment was examiner-rated time-to-ON with carbidopa/levodopa + CVT-301 vs carbidopa/levodopa + placebo.

Results: Of the 36 patients (mean age 62.9 years) who enrolled and completed the study, 9 (25.0%) reported treatment-emergent adverse events following CVT-301 administration; 4 (11.1%) reported treatment-emergent adverse events following placebo. The most common adverse event was cough (4 [11.1%] for CVT-301 vs 1 [2.8%] for placebo), which was typically mild and transient. Incidence of asymptomatic orthostatic hypotension (CVT-301, 6; placebo, 7) and examiner-rated dyskinesia were similar for both (36–39% mild, 3–6% moderate, and 0% severe). Median time-to-ON was 25.0 min following carbidopa/levodopa + CVT-301 and 35.5 min following carbidopa/levodopa + placebo ($P = 0.26$). At 30 min, more patients had turned ON following carbidopa/levodopa + CVT-301 administration (66.7%), compared with carbidopa/levodopa + placebo (44.5%) ($P = 0.040$).

Conclusion: Single doses of CVT-301 84 mg administered with oral carbidopa/levodopa for early morning OFF symptoms were well-tolerated, with no notable safety concerns.

1. Introduction

CVT-301 (Inbrija™) is a self-administered, orally inhaled levodopa (LD) formulation approved in the US for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa (CD)/LD. Prior studies only evaluated CVT-301 in patients on oral CD/LD therapy after the first ON of the day, when CD levels are presumed to be adequate to afford sufficient decarboxylase inhibition to minimize peripheral dopamine side effects from LD such as nausea/vomiting and orthostatic hypotension. The purpose of this study was to evaluate the acute safety and tolerability of CVT-301 given with the first oral CD/LD dose of the day, during early morning OFF, when plasma levels of CD may be low or nonexistent following an overnight break in oral CD/LD administration.

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Oral LD administered with a dopa decarboxylase inhibitor such as CD is the standard and most effective treatment for managing the motor symptoms of PD [1–3]. As the disease progresses, however, many patients begin to experience motor fluctuations, wherein symptoms are controlled (ON periods) and then re-emerge (OFF periods) [3–6]. Early morning OFF periods, or "morning akinesia," are common, difficult to treat, and associated with decreased quality of life [7–10]. Morning OFF periods reflect the decline in dopamine levels overnight during sleep and the delayed onset of efficacy of the first morning CD/LD dose, due to the time necessary for orally administered LD to reach the small intestine, travel from gut to blood, blood to brain, undergo decarboxylation to dopamine, and provide benefit at dopamine receptors. Delayed gastric emptying and competition with ingested protein can further prolong morning OFF periods [11,12].

CVT-301 bypasses the gastrointestinal tract and enters the circulatory system rapidly and predictably [13,14]. In a crossover study in patients with PD, plasma LD concentrations increased more rapidly after CVT-301 inhalation and with less variability in concentration than after oral CD/LD dosing, and in a pivotal phase 3 study it met the primary endpoint, improving the change in UPDRS-III score at 30 min post-dose compared with placebo at week 12, when administered during an OFF period [15]. The adverse events (AEs) and safety profile of CVT-301 were consistent with earlier studies [13,14]. However, treatment of early morning OFF symptoms was specifically excluded in these studies.

This current study was specifically designed to evaluate the immediate safety and tolerability of CVT-301 when administered for early morning OFF as inhaled LD does not contain CD and use of CVT-301 for early morning OFF has not been previously investigated. CD blocks the conversion of LD to dopamine in the periphery and reduces the likelihood of AEs such as orthostatic hypotension, vomiting, and nausea [3,16]. However, CD has a plasma half-life of approximately 2.5 h, so the concentration of CD in the blood after an overnight 8- to 12-h dose interruption is reduced to approximately 1/8 of its maximum [17]. Since CVT-301 does not contain CD, there is a possibility that taking CVT-301 in the early morning might trigger LD-associated AEs if a patient's CD plasma level has fallen below therapeutic levels. CVT-301 taken in the morning with the first oral CD/LD dose of the day may also yield a different safety and efficacy profile than CVT-301 taken during an OFF period following daytime CD/LD administration. The primary objective of this study was to investigate the safety and tolerability of CVT-301 84 mg when administered with the first oral dose of CD/LD of the day to treat early morning OFF symptoms. An exploratory efficacy objective was to determine the time required to reach an ON state with CVT-301 compared with placebo, when administered with the first oral CD/LD dose of the day.

2. Methods

This was a double-blind, placebo-controlled, randomized, 2-way crossover safety study in patients with PD who were on a stable regimen of PD medications prior to screening and remained on the regimen until completion of the 2 dosing days. On each dosing day, patients with PD in an early morning OFF state received a single dose of study drug immediately after taking their first oral dose of standard PD medication and were evaluated for safety, tolerability, and exploratory efficacy outcomes for 3 h.

The study was conducted at 11 sites in the US and was performed in accordance with the Declaration of Helsinki. All sites received IRB approval and all patients provided written informed consent prior to participation (clinicaltrials.gov NCT02807675). Safety assessments were collected by trained site personnel; efficacy assessments were made by the investigator or sub-investigator who were licensed physicians.

Patients were randomized 1:1 to one of 2 treatment sequences: either CVT-301 followed by placebo, or the reverse. Randomization was by an interactive voice recognition system (IVRS), except for 1 enrolled patient who was randomized manually prior to the activation of the IVRS.

Study duration was up to 39 days and included a screening period of up to 21 days. There were 2 dose administration/observation days separated by an interval of 1–7 days, and a follow-up phone call approximately 1 week after the final study visit.

2.1. Study population

Study participants were aged 30–85 years; diagnosed with PD at modified Hoehn and Yahr [18] stage 1–3 (while ON); and were on a stable regimen of standard PD medications for at least 30 days prior to screening. Other selection criteria included: forced expiratory volume in 1 s (FEV_1) ≥60% of predicted for race, age, sex, and height, and FEV_1/forced vital capacity ratio ≥70%; normal cognition (score ≥25 Mini-Mental State Examination [19] in the ON state); and experiencing ≥2 h of average daily OFF time per waking day (not including early morning OFF time). Patients were excluded if they had participated in any prior CVT-301 study; a history of symptomatic orthostatic hypotension, severe dysautonomia, or chronic obstructive pulmonary disease, asthma, or other chronic respiratory disease within the last 5 years; or previous surgery for PD (including, but not limited to, deep brain stimulation or cell transplantation).

2.2. Dosing

On the 2 dosing days at the study site, while in an early morning OFF state, patients self-administered CVT-301 or placebo immediately after taking their first oral CD/LD dose of the day. Elapsed time between the last oral dose of CD/LD of the previous night and the patient's first morning oral dose was at least 8 h. Each dosing day was separated by 1–7 days, while patients continued their standard CD/LD therapy.

Dopamine agonists, COMT inhibitors, MAO-B inhibitors, and other non-LD–containing PD medication doses were permitted but must have been stable for at least 4 weeks prior to screening. Antidepressants were also permitted, provided the dose had been stable for at least 4 weeks before screening. Oral PD medications taken as needed were permitted only during the screening period. The morning dose of these medications was given just prior to inhaled CVT-301; any other PD medications were not allowed for the next 3 h. Apomorphine was not permitted during the study and must not have been used for at least 4 weeks prior to the screening visit. Antipsychotic medications must not have been used for at least 12 months and were not allowed during the study. One patient was on low-dose quetiapine, prescribed for a non-psychosis–related condition and the dose had been stable for at least 1 month prior to screening.

2.3. Study medications

CVT-301 was supplied in capsule form, with each capsule containing 42 mg LD. Two capsules were administered sequentially via a CVT-301 inhaler to provide a total dose of 84 mg LD. Placebo control of 10 mg nonrespirable lactose monohydrate was selected for this study in order to provide the greatest potential difference in possible AEs when compared with inhaled LD at a time when CD levels are low. Nonrespirable lactose allows for the sensation of orally inhaling a powder but generally does not enter the lungs. Placebo was administered in the same manner as active medication using the identical capsule type. Patients were trained to use the inhaler by clinic staff.

2.4. Clinical outcome measures

Safety was evaluated in all patients who received at least 1 dose of any study medication by parameters that included AEs, serious AEs, routine and orthostatic vital signs, clinical laboratory and

electrocardiographic assessments, self-reported and examiner-rated dyskinesia, and evaluation of suicidal ideation and behavior via the Columbia-Suicide Severity Rating Scale (C-SSRS) [20].

For examiner-rated dyskinesia, the examiner recorded the occurrence of dyskinesia not more than 30 min before the oral CD/LD dose, and then at 10, 20, 30, 40, and 50 min after dosing. During the second and third hours post-dose, occurrence of dyskinesia was recorded every 15 min. Examiners also recorded the severity of dyskinesia when present. In a PD diary, patients recorded their waking PD state as OFF, ON without dyskinesia, ON with nontroublesome dyskinesia, or ON with troublesome dyskinesia [21]. On dosing days, patients completed their PD diary 30 min prior to the first morning oral CD/LD dose and then every 30 min subsequently for a 3-h period following the inhalation dose.

Examiner-rated times-to-ON were assessed as an exploratory efficacy endpoint. The examiner recorded the length of time to achieve an ON state in the 3 h following the inhaled dose, as reported by the patient and confirmed by the examiner. At the initial screening visit, patients underwent standard training and concordance testing for self-rating of the OFF state, ON state, and dyskinesia using a PD diary [21].

2.5. Pharmacokinetic measurements

Blood samples were taken to determine plasma concentrations of CD just prior to patients taking their first morning oral CD/LD dose on the day before the dosing period. At least 8 h were to have elapsed since their previous oral CD/LD dose.

2.6. Statistical analysis

Safety and tolerability data were presented using descriptive statistics. The duration of each dyskinesia response from the PD diary data obtained during the 3 h post-dose was summarized by treatment. The duration was derived based on the number of 30-min timepoints for which that result was reported. The maximum severity of examiner-rated dyskinesia was summarized by treatment and timepoint.

Exploratory efficacy analyses were performed on the intent-to-treat population. The efficacy variable was examiner-rated time-to-ON. Treatment comparisons (CVT-301 and placebo) were performed using an extension of the Wilcoxon-Gehan rank-sum test for crossover data. The percentage of patients achieving ON was analyzed using a non-parametric Prescott's test. No formal sample size calculation was performed for this trial. The number of patients was considered sufficient to meet the objectives of the study. The overall type 1 error rate was not adjusted for the exploratory efficacy analyses. All computations were performed using Statistical Analysis Software (SAS®) Version 9.4 (SAS Institute, Cary, NC).

3. Results

Forty-nine patients were screened and 36 were enrolled and completed the study. The patient population was primarily white (94.4%), male (58.3%), and had a mean duration of PD of 7.9 years (range 1.4–15.3 years), with acceptable pulmonary function (Table 1). At baseline, 13.9% of patients were taking adjunctive COMT inhibitors, 52.8% were taking dopamine agonists, 41.7% MAO-B inhibitors, and 25.0% amantadine.

Patients self-administered their morning oral CD/LD dose between 8.7 and 17.7 h after their last oral dose. The mean and median durations between the morning oral CD/LD doses and the oral CD/LD doses administered the previous evenings were 10.8 h (SD ± 1.98) and 10.3 h, respectively.

Table 1
Baseline and demographic characteristics.

Demographic	Overall (N = 36)
Age (y), mean (range)	62.9 (39–81)
Gender, n (%)	
Male	21 (58.3)
Female	15 (41.7)
Race, n (%)	
White	34 (94.4)
Asian	2 (5.6)
Ethnicity, n (%)	
Hispanic/Latino	16 (44.4)
Non-Hispanic/Latino	20 (55.6)
Body weight (kg), mean (SD)	79.3 (16.8)
BMI (kg/m^2), mean (SD)	28.2 (5.9)
% predicted FEV_1, mean (range)	93.9 (73–114)
% predicted FEV_1/FVC, mean (range)	105.8 (96–120)
MMSE, mean (range)	28.8 (25–30)
Duration of PD (y), mean (range)	7.9 (1.4–15.3)
LD daily dose (mg), mean (SD)	727.5 (272.0)
LD morning dose (mg), mean (SD)	183.8 (124.4)[a]
Hoehn & Yahr stage, n (%)	
1	2 (5.6)
2	16 (44.4)
2.5	8 (22.2)
3	10 (27.8)
Other PD-drug use, n (%)	
COMT inhibitors	5 (13.9)
Dopamine agonists	19 (52.8)
Ropinirole	5 (13.9)
Rotigotine patch	7 (19.4)
Pramipexole	5 (13.9)
Pramipexole dichloride	2 (5.6)
MAO-B inhibitors	15 (41.7)
Adamantanes	9 (25.0)
Amantadine	8 (22.2)
Amantadine HCl	1 (2.8)

BMI, body mass index; COMT, catechol-O-methyltransferase; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCL, hydrochloride; LD, levodopa; MAO-B, monoamine oxidase type B inhibitor; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; SD, standard deviation.

[a] Oral LD dose taken prior to first dose of study medication.

3.1. Safety

3.1.1. Adverse events

Twelve patients experienced 17 treatment-emergent AEs (TEAEs) during the study, 9 (25%) patients with 12 AEs after CVT-301 administration, and 4 (11.1%) patients with 5 AEs after placebo. There were no deaths, serious AEs, or AEs that led to discontinuation. Two TEAEs, palpitations and hypertension, occurred in 1 patient following administration of CVT-301. These were moderate in severity and were assessed as unrelated to CVT-301 by the investigator. All other TEAEs were mild. All TEAEs resolved without treatment, except in 2 patients who were prescribed ibuprofen for headache.

The overall incidence of TEAEs classified as related to CVT-301 is shown in Table 2.

Cough was the most frequently reported TEAE. All cough AEs were reported as mild. Cough following administration of CVT-301 occurred up to 1 min post-dose and lasted for between 5 and 11 min.

When measured between 8.4 and 15.3 h following the last oral CD/LD dose, the mean plasma concentration of CD was 32.4 µg/L (SD ± 29.2), with a range of < 10.0 µg/L (lower limit of quantification) to 116.0 µg/L. The frequency of occurrence of TEAEs in relation to CD concentration was examined and there appeared to be no clear relationship between AEs and CD trough concentrations. There also was no clear relationship between AEs and trough concentrations when cough AEs were excluded from the analysis.

Table 2
Frequency of TEAEs possibly or probably related to CVT-301.

Adverse Event	Placebo (n = 36)		CVT-301 84 mg (n = 36)		Overall (n = 36)	
	Patients, n (%)	AEs, n	Patients, n (%)	AEs, n	Patients, n (%)	AEs, n
Overall	2 (5.6)	3	7 (19.4)	8	9 (25.0)	11
Cough	1 (2.8)	1	4 (11.1)	4	5 (13.9)	5
Yawning	0	0	1 (2.8)	1	1 (2.8)	1
Nausea	1 (2.8)	1	1 (2.8)	1	2 (5.6)	2
Dizziness	1 (2.8)	1	0	0	1 (2.8)	1
Somnolence	0	0	1 (2.8)	1	1 (2.8)	1
Hyperhidrosis	0	0	1 (2.8)	1	1 (2.8)	1

TEAEs, treatment-emergent adverse events.

3.1.2. Examiner-rated dyskinesia

Patients were assessed for the occurrence of dyskinesia during the first 3 h post-dose by the investigator or qualified designee. The majority of patients had no dyskinesia immediately prior to administration of CD/LD with either CVT-301 or placebo (> 91%). During the 3 h following CD/LD administration with CVT-301 or placebo, 12 (33.3%) and 13 (36.1%) patients, respectively, changed from having no dyskinesia to having any dyskinesia (mild or moderate) (Fig. 1A). Only 2 patients had dyskinesia recorded following administration of CVT-301 but not placebo, and only 2 patients had dyskinesia recorded following administration of placebo but not CVT-301. No patients had severe dyskinesia pre- or post-dose. There was no clear relationship between dyskinesia and CD concentrations.

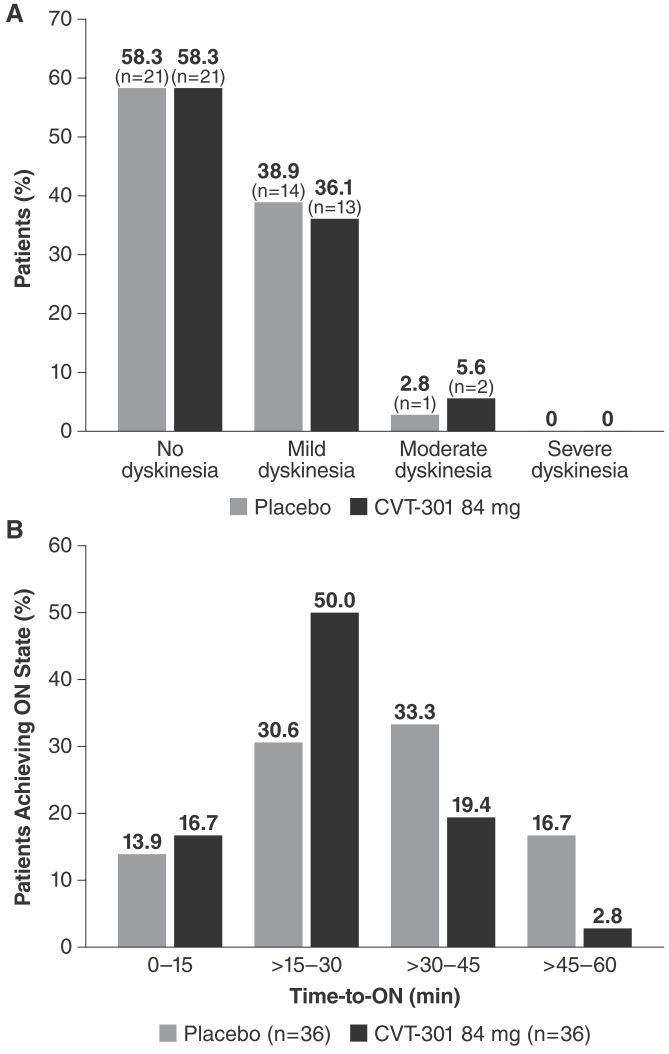

Fig. 1. A. Examiner-rated dyskinesia for 3 h post-dose. B. Percentage of patients achieving ON during 1-h post-dose.

3.1.3. Other safety measures

There were no apparent treatment-related trends in routine vital signs or in orthostatic vital signs data following CVT-301 administration, and no apparent trends in these events with respect to time post-dose. Orthostatic hypotension was defined as a reduction in systolic blood pressure of ≥20 mmHg, and/or a reduction in diastolic blood pressure of ≥10 mmHg after standing for at least 2 min from a semi-supine position. Thirteen events occurred in 9 patients with 6 events occurring after administration of CD/LD plus CVT-301 and 7 after CD/LD plus placebo. Of the 9 patients who experienced orthostatic hypertension, 4 experienced the event after both CVT-301 and placebo administration. These events were asymptomatic, not associated with any relevant AEs (eg, dizziness, syncope, nausea), and were not considered to be clinically significant. Three of the patients with orthostatic hypotension had a medical history of hypertension and were being treated with lisinopril, enalapril, or metoprolol. No patients reported suicidal ideation or demonstrated suicidal behavior following CVT-301 dosing, as reported on the C-SSRS.

3.2. Exploratory efficacy assessments

While this study was not powered to evaluate efficacy, the following assessments were included to assess any clinical benefit that might suggest larger, appropriately powered studies should be performed.

3.2.1. Examiner-rated time-to-ON

The examiner-rated time-to-ON was assessed over 3 h post-dose and a nonsignificant treatment difference was noted ($P = 0.26$, Wilcoxon-Gehan rank-sum test) when comparing CVT-301 84 mg (median time-to-ON of 25.0 min [95% CI 22.0–30.0]) and placebo (the median time-to-ON of 35.5 min [95% CI 25.0–39.0]). A post hoc analysis of time-to-ON (Fig. 1B) shows the proportion of patients achieving ON at earlier timepoints was greater with CVT-301. By 30 min post-dose, 66.7% (n = 24) had turned ON following CVT-301 administration, compared with 44.5% (n = 16) following placebo. This difference was analyzed via Prescott's test ($P = 0.040$).

3.2.2. PD home diary

During the 3 h following dosing of either CVT-301 or placebo, the mean duration of ON without troublesome dyskinesia (combined ON without dyskinesia and ON with nontroublesome dyskinesia) was minimally longer for patients administered CVT-301 than placebo (148.8 and 144.0 min, respectively [Table 3]). One patient experienced an ON period with troublesome dyskinesia in the 3 h post-dose following placebo administration. The mean duration of OFF was slightly greater in patients administered placebo (34.8 min) than in those administered CVT-301 (30.0 min).

4. Discussion

This study addresses the concern that inhalation of CVT-301 in the early morning, immediately after the first oral CD/LD dose of the day, might be poorly tolerated due to low morning plasma levels of CD, leading to peripheral dopamine side effects such as orthostatic hypotension and nausea [3,16]. Results demonstrated that single doses of CVT-301 84 mg were generally well-tolerated in a group of patients with early morning OFF symptoms, whose previous evening oral dose of CD/LD was taken 8.7–17.7 h earlier. There were no apparent treatment-related trends in orthostatic vital signs and no apparent trends in events of orthostatic hypotension or nausea. The observed orthostatic hypotension was asymptomatic, was not more frequent after CVT-301

Table 3
Duration of ON and OFF states during the 3 h post-dose from the PD diary.

Mean (range), min	Placebo (n = 36)	CVT-301 84 mg (n = 36)
OFF	34.8 (0–120.0)	30.0 (0–180.0)
ON without dyskinesia	117.6 (0–180.0)	107.4 (0–180.0)
ON with nontroublesome dyskinesia	26.4 (0–150.0)	41.4 (0–180.0)
ON, combined (nontroublesome + without dyskinesia)	144.0 (0–180.0)	148.8 (0–180.0)
ON with troublesome dyskinesia	0.6 (0–30.0)	0 (0–0)

PD, Parkinson's disease.

administration, and was not associated with AEs such as dizziness, syncope, or nausea.

Cough was the most frequently reported TEAE following CVT-301 inhalation, which agrees with observations from previously published studies of CVT-301 [13,14,22]. All reported cough AEs were mild in severity and transient and did not lead to study discontinuation.

Dyskinesia was not more common when CVT-301 was added to patients' usual morning dose of CD/LD (21 patients [58.3%] for both CVT-301 and placebo). In the same number of patients, 15 (41.7%) had mild or moderate dyskinesia after either dose administration, and 2 patients experienced dyskinesia only after placebo, while 2 others reported dyskinesia only after CVT-301.

While this safety study was not powered to assess the exploratory efficacy endpoints, results suggest the possibility of clinical benefit. Median examiner-rated time-to-ON was about 10 min shorter after CVT-301, although this result was not statistically significant. A post hoc analysis showed that more patients had turned ON 30 min after CVT-301 inhalation, compared with placebo. Whether increasing the morning oral CD/LD would provide a similar effect is not known. Although effects between the 2 groups in our study were similar according to the PD diary data (Table 3), diaries are probably not sufficiently sensitive to pick up changes over such a short time period. Assessing the efficacy of CVT-301 when used for early morning OFF episodes specifically should be addressed with longer-term and appropriately powered studies.

Common clinical approaches to treating morning akinesia are empiric, such as taking a CD/LD dose very early before getting up, using a higher morning CD/LD dose, dissolving and taking liquid CD/LD, or taking CD/LD with a carbonated beverage. Alternatively, some patients use a subcutaneous injection of apomorphine [23]. Determining whether CVT-301 provides clinical benefit for early morning OFF would require a larger, adequately powered trial. We note that the current trial was designed to assess the safety of CVT-301 versus placebo as an adjunct to the patient's usual morning dose of CD/LD. It did not compare the addition of CVT-301 to using a higher morning oral CD/LD dose or to the use of subcutaneous injection of apomorphine.

In this study, single inhaled doses of CVT-301 84 mg taken during an early morning OFF period together with routine oral CD/LD therapy were well-tolerated by patients with PD and produced no serious TEAEs.

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Authors' roles

Research project

Conception: RAH, CO, SFK, DMK-E, PZ.
Organization: CO, SFK.
Execution: RAH, SHI, AE, BES, DDT.
Data and statistical analysis: RAH, SHI, AE, BES, DDT, SFK, DMK-E, PZ, CO.
Manuscript: RAH, SHI, AE, BES, DDT, SFK, DMK-E, PZ, CO.

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