Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background Patients with Parkinson's disease chronically treated with levodopa commonly have delayed or unpredictable onset of its benefits after oral intake. In this study, we assessed the safety and efficacy of CVT-301, a self-administered levodopa oral inhalation powder, for the treatment of patients with Parkinson's disease during off periods.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, patients were recruited at 65 sites in Canada, Poland, Spain, and the USA. Eligible participants were patients with Parkinson's disease aged 30–85 years, who had daily off periods of 2 h or longer and showed an improvement of 25% or greater in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score from off to on state after use of an oral levodopa plus a dopa-decarboxylase inhibitor combination. Patients were assigned (1:1:1) with a computer-generated randomisation code, in fixed blocks of six, to either CVT-301 60 mg, CVT-301 84 mg, or placebo. Spirometry results and modified Hoehn and Yahr disease stage at screening were used for stratification of treatment groups. Patients, the sponsor, and site personnel were masked to treatment assignment. Each study dose consisted of two capsules administered with an inhaler. Patients were instructed to use the study drug as needed for off periods, and could self-administer up to five doses per day. The primary endpoint was the change in UPDRS motor score from predose to 30 min postdose, assessed at week 12 during an in-clinic off period, in the CVT-301 84 mg group compared with the placebo group. Analysis was by intention to treat. Safety was assessed in all patients who received at least one dose of experimental treatment. This trial is registered with ClinicalTrials.gov, number NCT02240030.

Findings Between Dec 4, 2014, and Aug 26, 2016, 351 patients were enrolled and randomly assigned to receive CVT-301 60 mg (115 patients), CVT-301 84 mg (120 patients), or placebo (116 patients). Of these, 339 received the assigned study treatment (CVT-301 60 mg, n=113; CVT-301 84 mg, n=114; placebo, n=112) and 290 completed the study (CVT-301 60 mg, n=96; CVT-301 84 mg, n=97; placebo, n=97). The least-squares mean difference in UPDRS motor score change from predose to 30 min postdose was –5·91 (SE 1·50, 95% CI –8·86 to –2·96) for the placebo group and –9·83 (1·51; –12·79 to –6·87) for the CVT-301 84 mg group (between-group difference –3·92 [–6·84 to –1·00]; p=0·0088). Treatments were safe and well tolerated. Severe adverse events were reported by 2 (2%) of 112 patients in the placebo group, 7 (6%) of 113 in the CVT-301 60 mg group, and 5 (4%) of 114 in the CVT-301 84 mg group, with no severe adverse event occurring in more than one patient in any treatment group. 11 (3%) of 339 patients had 19 serious adverse events (three [3%] of 112 patients in placebo, six [5%] of 113 in CVT-301 60 mg, and two [2%] of 114 in CVT-301 84 mg). Of these, hypotension and atrial fibrillation were assessed by investigators to be possibly related to the study drug.

Interpretation CVT-301 can improve UPDRS motor scores of patients with Parkinson's disease during in-clinic off periods, with few severe or serious adverse events. The long-term safety and efficacy of CVT-301 need to be investigated in future studies.

Funding Acorda Therapeutics.

Introduction

Of all available treatment options for Parkinson's disease, levodopa plus a dopa-decarboxylase inhibitor (LD-DCI) is the standard of care for symptomatic treatment.[1] Initial therapy with levodopa typically provides benefits lasting beyond the approximate levodopa clearance half-life of 2 h. However, after 2 years or more of continued treatment, the duration of the clinical response to levodopa typically shortens.[2] In such circumstances, symptom relief from each dose of levodopa wears off in a pattern that roughly

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Research in context

Evidence before this study

We searched PubMed for reports of clinical trials published in English up to Sept 17, 2018, with the search terms "CVT-301", "inhaled levodopa", "Parkinson's", "Parkinson", "motor fluctuations", "motor complications", "OFF periods", "OFF episodes", and "OFF state".

In a phase 2a, dose-finding, crossover study, 24 patients with Parkinson's disease received fine-particle doses of CVT-301 25 mg or 50 mg (ie, estimated pulmonary delivered dose) and standard oral carbidopa-levodopa. Plasma levodopa concentrations increased more rapidly and with less variability in the CVT-301 groups than in the oral levodopa group. The only adverse event reported by more than one patient was cough, and no serious or severe adverse events were reported. In a phase 2b safety and efficacy study, 89 patients with Parkinson's disease who had off periods despite a regular oral carbidopa-levodopa regimen were randomly assigned to CVT-301 or placebo for 4 weeks; after 2 weeks, the study drug was escalated from 35 mg to 50 mg fine-particle dose. At 4 weeks, least-squares mean change in unified Parkinson's disease rating scale (UPDRS) motor score and mean off-time change from baseline were significantly better in patients receiving CVT-301 than in those receiving placebo. The most frequently reported adverse events in the CVT-301 group were dizziness, cough, and nausea. Pulmonary function testing by spirometry over 4 weeks in both studies showed that findings were within normal ranges for both the CVT-301 and placebo groups. The conclusion from both studies was that CVT-301 treatment was not associated with acute airflow obstruction.

Added value of this study

This phase 3 study of CVT-301 showed results that support earlier findings that CVT-301 is safe and effective at improving UPDRS motor scores in patients with Parkinson's disease who have off periods. The primary endpoint of our study was met at the 12-week assessment (with the CVT-301 84 mg dose). The improvement in the UPDRS score (at 30 min postdose) is in accordance with the significantly greater percentage of patients who had and maintained an on response through 60 min after dosing.

Implications of all the available evidence

A rapid and reliable treatment for the reversal of off periods would fulfil an important unmet need for patients with Parkinson's disease who have off periods. The only available treatment is a subcutaneously administered dopaminergic agonist—apomorphine. However, apomorphine requires administration by injection and commonly requires concomitant administration of an antiemetic for nausea and emesis. Pulmonary absorption of CVT-301 is a promising development for treating off periods and, in the present study, CVT-301 achieved reliable improvement of off periods with few severe or serious adverse events and without increasing dyskinesia.

parallels the drug's pharmacokinetic profile.[3] Additionally, patients can have delayed effect, unpredictable effect, or no effect of levodopa, because of delayed gastric delivery of the drug to the proximal small intestine, where absorption is facilitated by an L-neutral amino acid transport mechanism.[4] Pharmacological strategies to extend the release of LD-DCI in the upper gastrointestinal tract or to slow the enzymatic metabolism of levodopa confer some benefits. However, delay of an on state (period of symptom control), off periods (return of symptoms), and dose failure due to irregular levodopa uptake are major unmet needs, affecting both motor features of advanced parkinsonism and non-motor symptoms.[5]

Among available pharmacotherapies for Parkinson's disease, the only marketed product for rapid reversal of off periods is apomorphine, a subcutaneously administered dopaminergic agonist. Apomorphine is generally underused by patients with Parkinson's disease because of its need for injection, frequent side-effects, and need for antiemetic drug premedication.[6] An alternative treatment option in development for treating off periods is the pulmonary delivery of CVT-301, an orally-inhaled levodopa powder formulation, which bypasses the gastrointestinal tract.[7] A phase 2 study[8] showed that CVT-301 provided reliable improvements in motor function and reduced the number of off periods in patients with Parkinson's disease experiencing motor fluctuations. Here, we present the results of a phase 3 study that aimed to investigate the safety and efficacy of CVT-301 in patients with Parkinson's disease with off periods.

Methods

Study design and participants

This study was a randomised, double-blind, placebo-controlled, multicentre, phase 3 study of CVT-301 delivered by oral inhalation, as an as-needed adjunct therapy to a daily LD-DCI regimen, for treatment of off periods in patients with Parkinson's disease. The study was done at 65 neurology clinics or specialised centres in four countries: four sites in Canada, eight in Poland, one in Spain, and 52 in the USA.

Eligible patients were aged 30–85 years and had Parkinson's disease diagnosis according to the UK Parkinson's Disease Association Brain Bank Criteria,[9] modified Hoehn and Yahr (MHY) disease stage 1–3 when in an on period, a Mini Mental State Examination[10] score of 25 or higher, a stable regimen of LD-DCI (either carbidopa or benserazide) for 2 weeks or longer before screening (6 weeks if receiving extended-release LD-DCI), at least three daily levodopa administrations for a total intake of 1600 mg or less, other Parkinson's disease medication unchanged for 4 weeks or longer before screening, motor fluctuations with an average daily off time of 2 h or longer (and with ≥25% improvement

between unified Parkinson's disease rating scale [UPDRS] motor score[11] from off to on state at screening), ability to do spirometry when in an on or off state, and forced 1-s expiratory volume (FEV_1) of 50% or higher and an FEV_1 to forced vital capacity (FVC) ratio of 60% or higher when in an on state. Key exclusion criteria were severe dyskinesia, previous neurosurgical treatment for Parkinson's disease, active psychosis or antipsychotic drug treatment, a history of drug or alcohol abuse, orthostatic hypotension, and chronic respiratory disease.

The protocol, patient information, consent form, and other relevant study documentation were approved by the Ethics Committees or Institutional Review Boards of each site before study initiation. The study was done in accordance with ethical principles originating from the Declaration of Helsinki and consistent with good clinical practice and applicable regulatory requirements. Before enrolment, all patients provided written informed consent.

The study protocol can be accessed online.

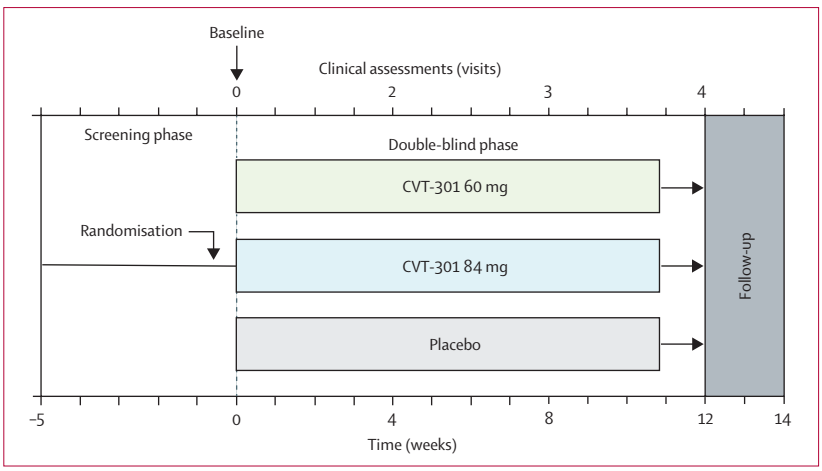

Figure 1: **Study design**

Randomisation and masking

Patients entering the double-blind part of the study were randomly assigned (1:1:1), within a fixed block size of six, to one of two treatment groups or to the placebo group. To balance disease severity, randomisation was stratified by MHY scale category (<2·5 *vs* ≥2·5), assessed in patients during on state. We also used screening spirometry results for two stratification groups: FEV_1 lower than 60% of predicted or FEV_1 to FVC ratio lower than 70% versus FEV_1 of 60% or higher than predicted and FEV_1 to FVC ratio of 70% or higher. Treatment was randomised by a computerised software program (SAS Institute) and assigned by the study site contact with an interactive web response system holding the masked assignment codes. An independent biostatistician from the contract research organisation (Syneos Health, Morrisville, NC, USA) generated the randomisation codes in a folder with restricted access; these codes were uploaded to a centralised interactive web response system. This biostatistician was independent from the study biostatistician, and a firewall was in place to maintain independence.

Patients, the study sponsor, and site personnel were masked to treatment assignment. To maintain blinding of administered study drug, capsules for each of the three possible study treatments (two doses of CVT-301 or placebo) were identical in appearance, and packaging was labelled in a manner that did not reveal which treatment the capsules contained. Patients, investigators, study site personnel, the sponsor, Core Laboratories (Amsterdam, Netherlands), and representatives of Syneos Health involved in monitoring, data management, or other aspects of the study were masked to the inhaled study treatment. Study kits with identical number and capsule appearance were distributed to patients. Study treatment codes were not available to the investigators, the study site personnel, representatives of Syneos Health, or the sponsor during the conduct of the study. If emergency unblinding became necessary, the interactive web response system included a method to disclose this information, but this was not done for any patient in the study. Study drug codes were made available for data analysis after completion of the study, verification of data files, and determination of protocol violations. The initial dose of masked study drug was administered in-clinic at the first treatment visit.

For the **study protocol** see http://www.acorda.com/assets/docs/cvt-301-004-protocol-version-5-0.pdf

Procedures

Patients received CVT-301 60 mg, CVT-301 84 mg, or placebo. Both doses and placebo consisted of two capsules: the CVT-301 60 mg dose capsules were filled with 30 mg of study drug and provided a respirable fine-particle dose of 17·5 mg each, whereas the CVT-301 84 mg dose capsules were filled with 42 mg of study drug and provided a respirable fine-particle dose of 25 mg each. CVT-301, a fine-powder formulation consisting of levodopa (90% of total weight), dipalmitoyl phosphatidylcholine (the primary constituent of endogenous lung surfactant), and sodium chloride, was administered by an inhaler with the ARCUS pulmonary delivery system (Acorda Therapeutics, Chelsea, MA, USA).[7] Each of the two capsules was placed sequentially into the device and was punctured during an actuation process, allowing the patient to inhale the capsule's contents. Placebo capsules contained 10 mg of inhalation-grade, non-respirable lactose that generally does not enter the lung but allows for the sensation of orally inhaling a powder. The inhaler was designed for competent use by patients with Parkinson's disease in an off period, even when they might be having diminished dexterity.[7]

Study participants were screened during a 5-week screening period (with two visits 4 days or more apart), then underwent a 12-week treatment period (with visits at baseline and at 4, 8, and 12 weeks). At the end of the double-blind treatment phase, patients were offered either participation in a long-term extension study or were followed up for a further 1 to 2 weeks (figure 1).

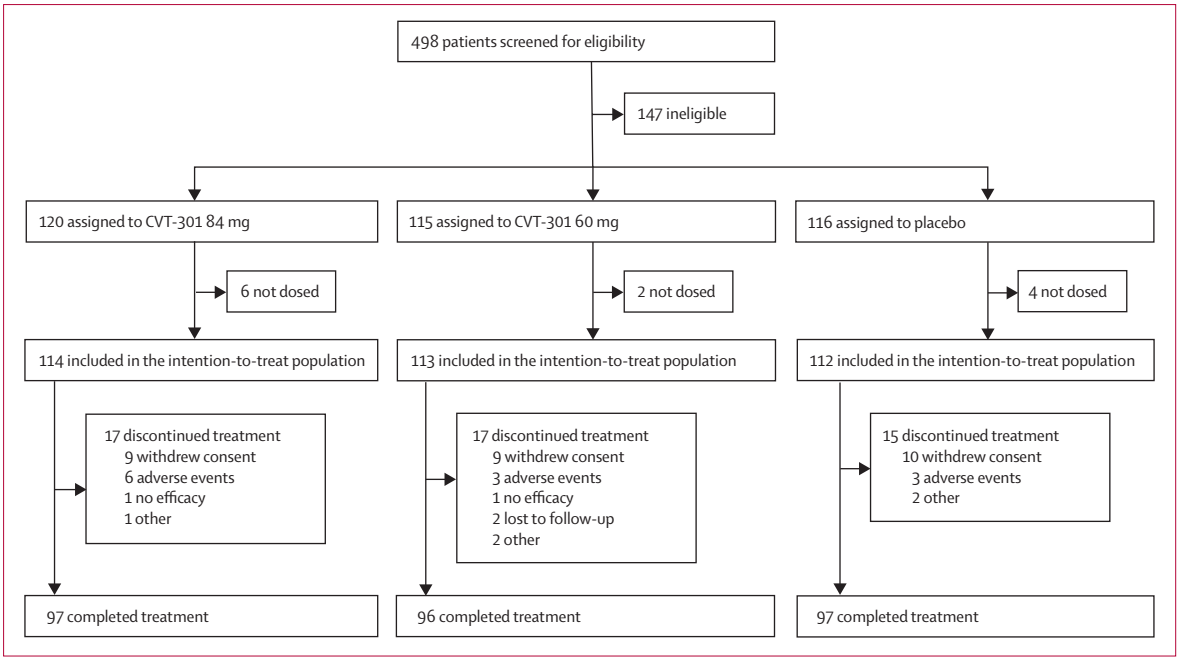

Figure 2: **Trial profile**

During the screening visits, patients were trained to use the CVT-301 inhaler. Before randomisation and the first self-administration at baseline visit, all patients needed to demonstrate they were capable of using the inhaler when experiencing an off period. During the 12-week treatment period, patients self-administered the study drug during clinic visits and, as outpatients, on an as-needed basis for off periods. Patients were instructed to self-administer the study drug up to five times during the day, as close as possible to when they began to have off-period symptoms, which could be motor or non-motor. The study drug was not to be used for the treatment of early morning off periods (ie, morning akinesia) before the first oral dose of LD-DCI. Patients were instructed to use a single dose (two capsules) per off period and not to take oral medications as needed to manage off periods while taking the study drug. If an off state was not sufficiently resolved within 45 min of completing the last capsule inhalation, patients were to resume their usual prescribed Parkinson's disease medication. Apomorphine injections were prohibited throughout the study.

Study assessments included in-clinic UPDRS scoring and a diary for patients to complete at home.[12] For 3 days before each clinic visit, patients recorded whether they were predominantly in an off or on state during waking hours at 30-min intervals. For on state assessments, patients indicated if they had dyskinesias and, if so, whether they were troublesome or not. Patients also recorded a seven-element Patient Global Impression of Change (PGI-C) scale score regarding Parkinson's disease symptoms. With each inhalation, patients were instructed to take a deep and comfortable breath that was held in for about 5 s. For timing study assessments during a dosing visit, time 0 was defined as the start of the final breath-hold with the last capsule of inhaled study treatment.

Outcomes

The primary endpoint was the effect of CVT-301 84 mg compared with that of placebo on change in UPDRS motor scores from predose to 30 min postdose, assessed at week 12 during an in-clinic off period. Key secondary endpoints for CVT-301 versus placebo were also assessed at week 12 in a hierarchical order that was based on previous findings from a phase 2 study. These endpoints were as follows: proportion of patients who achieved and maintained an on state up to 60 min after receiving study medication in the clinic, as assessed by study personnel; change in UPDRS motor score from predose to 20 min postdose, as assessed by study personnel; proportion of patients who self-reported improvement in the PGI-C rating scale; change in UPDRS motor score from predose to 10 min postdose, as assessed by study personnel; and change in total daily off-state time from baseline to the mean of 3 consecutive days before the week 12 visit, with data entered by patients into a home diary. The primary and secondary endpoints were analysed according to this sequence for the CVT-301 84 mg dose and, subsequently, in the same order for the 60 mg dose. Data for all secondary endpoints were collected at weeks 4, 8, and 12.

At all treatment visits and at the follow-up visit, we assessed treatment-emergent adverse events, serious and severe adverse events, clinical laboratory values,

electrocardiograms (ECGs), physical examinations, and vital signs data (sitting and standing). A serious adverse event was defined as any adverse event that poses a threat to a patient's life or functioning and that met one or more of the following criteria: resulted in death, was life threatening, resulted in unplanned inpatient hospitalisation or prolonged an existing hospitalisation, causes a congenital anomaly, caused substantial incapacity or disability, or was an important medical event that required medical intervention of any kind to prevent any of the aforementioned outcomes. The severity of adverse events (mild, moderate, or severe) was assessed by the investigators.

Spirometry (consisting of FEV_1, FEV_1 to FVC ratio, and carbon monoxide diffusing capacity) was assessed before randomisation, and at weeks 6 and 11. Pulmonary function was measured using the guideline specified by the Third National Health and Nutrition Examination Survey.[13]

Statistical analysis

For the primary analysis, we used a mixed model for repeated measures to estimate differences in change from predose UPDRS motor scores between the CVT-301 84 mg and placebo groups at week 12. The model included the following fixed factors: treatment group, visit, stratification variables (MHY stage and FEV_1 to FVC ratio at screening), and interaction between visit and treatment group. The off-state baseline UPDRS motor score was included as a covariate. The 10 min, 20 min, 30 min, and 60 min postdose timepoints were estimated by separate mixed models for repeated measures.

For secondary endpoints, we analysed continuous variables with a mixed model for repeated measures similar to that used for the primary analysis. However, the baseline assessment value of the variable was a covariate instead of the off-state baseline UPDRS motor score. Categorical variables were analysed using the Cochran-Mantel-Haenszel test stratified by MHY stage and by screening FEV_1 values, FEV_1 to FVC ratio, or both.

The primary and key secondary endpoints assessing the effect of CVT-301 versus placebo at week 12 were tested first for the CVT-301 84 mg dose and then for the CVT-301 60 mg dose in a hierarchical manner that maintained an overall $\alpha=0\cdot05$ (and adjusted for high-dose and low-dose comparisons *vs* placebo). The testing continued only if the previously ranked endpoint was statistically significant at $p<0\cdot05$.

We did six prespecified sensitivity analyses for the primary endpoint: a mixed model for repeated measures based on the population of patients who completed treatment; a multiple imputation analysis with missing-at-random assumption; a multiple imputation analysis with missing-not-at-random assumption; a mixed model for repeated measures with added region effect (Europe *vs* North America); a mixed model for repeated measures with added interaction between region and treatment group; and a mixed model for repeated measures analysis of average change from predose in the UPDRS part 3 score at 30 min to postdose at week 4, week 8, and week 12 visits.

We determined sample size on the basis of the primary endpoint. The study was powered to detect a difference of

	CVT-301 84 mg (n=114)	CVT-301 60 mg (n=113)	Placebo (n=112)
Age, years	63·5 (7·97)	63·9 (9·24)	62·6 (8·83)
Sex			
Men	83 (73%)	80 (71%)	86 (77%)
Women	31 (27%)	33 (29%)	26 (23%)
Race			
White	107 (94%)	107 (95%)	107 (96%)
Black	4 (4%)	3 (3%)	0 (0%)
Asian	2 (2%)	0 (0%)	4 (4%)
Other	1 (1%)	2 (2%)	1 (1%)
Body-mass index, kg/m²	27·43 (4·66)	27·19 (4·81)	27·63 (5·33)
MMSE total score	29·0 (1·3)	28·6 (1·5)	28·8 (1·5)
Time since diagnosis, months	95·7 (46·3)	104·3 (56·4)	97·4 (54·10)
Disease severity			
Modified Hoehn and Yahr stage <2·5	72 (63%)	74 (65%)	74 (66%)
Modified Hoehn and Yahr stage ≥2·5	42 (37%)	39 (35%)	38 (34%)
Smoking history			
Never smoked	65 (57%)	75 (66%)	72 (64%)
Former smoker	44 (39%)	38 (34%)	37 (33%)
Current smoker	5 (4%)	0 (0%)	3 (3%)
Spirometry at screening			
FEV_1 <60% or FEV_1 to FVC ratio <70%	7 (6%)	6 (5%)	6 (5%)
FEV_1 ≥60% and FEV_1 to FVC ratio ≥70%	107 (94%)	107 (95%)	106 (95%)
Levodopa treatment			
Duration of treatment, months	75·0 (44·6)	84·8 (54·6)	81·6 (53·6)
Levodopa dosage, mg/day	818·6 (401·0)	822·7 (364·1)	841·4 (396·5)
Levodopa doses, number per day	5·0 (1·6)	5·0 (1·7)	5·2 (1·9)
UPDRS part 3 score at screening			
Off state	33·0 (11·0)	35·0 (10·3)	35·4 (12·4)
On state*	14·9 (7·4)	15·8 (8·0)	16·1 (8·3)
Off periods†			
Number per day	3·58 (1·09)	3·54 (1·24)	3·28 (1·10)
Total off time per day, h	5·35 (2·26)	5·60 (1·90)	5·59 (2·25)
Dyskinesia‡			
Patients dyskinetic before baseline	53 (46%)	43 (38%)	46 (41%)
Patients non-dyskinetic before baseline	61 (54%)	70 (62%)	66 (59%)
Other Parkinson's disease drug use			
Dopaminergic agonists	69 (61%)	76 (67%)	61 (54%)
Monoamine oxidase-B inhibitors	45 (39%)	34 (30%)	43 (38%)
Catechol-O-methyltransferase inhibitors	17 (15%)	19 (17%)	15 (13%)
Amantadine	23 (20%)	25 (22%)	22 (20%)

Data are mean (SD) or n (%). MMSE=Mini mental state exam. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. UPDRS=Unified Parkinson's Disease Rating Scale. *Data were missing for one patient from the CVT-301 84 mg dataset. †Data from the Parkinson's disease home diary at screening. ‡Patients with dyskinesia were defined as those who recorded at least 1 h of dyskinesia (on state with non-troublesome dyskinesia, or on state with troublesome dyskinesia) on at least 2 days before baseline.

Table 1: **Patient baseline demographic and disease characteristics**

	Hierarchical step	CVT-301 84 mg *vs* placebo		Hierarchical step	CVT-301 60 mg *vs* placebo	
		(95% CI)	p value		(95% CI)	p value
Change in UPDRS motor score at 30 min, LS difference*	1	−3·92 (−6·84 to −1·00)	0·0088	7	−3·07 (−5·99 to −0·16)	0·039
Responder on state at 60 min, odds ratio	2	2·65 (1·48 to 4·76)	0·0027	8	2·30 (1·29 to 4·10)	0·006
Change in UPDRS motor score at 20 min, LS difference	3	−2·55 (−5·22 to 0·13)	0·062	9	−1·98 (−4·65 to 0·70)	0·147
Improvement on PGI-C, odds ratio	4	2·94 (1·62 to 5·33)	<0·001	10	1·85 (1·05 to 3·28)	0·026
Change in UPDRS motor score at 10 min, LS difference	5	−2·26 (−4·48 to −0·04)	0·046	11	−0·97 (−3·19 to 1·24)	0·387
Change in Parkinson's disease diary off-state time, LS difference	6	−0·01 (−0·55 to 0·56)	0·975	12	−0·10 (−0·66 to 0·46)	0·722

UPDRS =Unified Parkinson's Disease Rating Scale. LS=least-squares mean. PGI-C=patient global impression of change. *Primary endpoint.

Table 2: **Efficacy analysis at week 12 by hierarchical endpoints**

5 points in mean change in the average UPDRS motor score, assuming an SD of 10·0 points. 86 patients per group were required to achieve 90% power at a two-sided significance of p<0·05. To account for a drop-out of about 25%, 115 patients per group were randomly assigned to treatment. If the withdrawal exceeded 25%, additional patients could be enrolled to ensure that at least 258 patients completed the study. Primary endpoint and secondary analyses were done in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of the study treatment. An independent data safety monitoring board reviewed the safety data. Statistical analyses were done with SAS program, version 9.3.

The trial is registered with ClinicalTrials.gov, number NCT02240030.

Role of the funding source

The study was funded and conducted by Acorda Therapeutics, Inc, who was responsible for data collection, monitoring, and statistical analysis. Acorda participated in the study design, reviewed the manuscript, and provided comments for consideration by the authors. Data collection was coordinated by the sponsor and designates, who also conducted the study. Acorda also supported reporting of study results as employer of three coauthors and by providing funding for editorial support; none of the remaining authors received payment. All final content decisions were made by the authors, who had full access to all of the study data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Dec 4, 2014, and July 29, 2016, 498 patients with Parkinson's disease were screened, 147 were deemed ineligible, and, by Aug 26, 2016, 351 were enrolled and randomly assigned to receive CVT-301 60 mg (115 patients), CVT-301 84 mg (120 patients), or placebo (116 patients). Two patients in the CVT-301 60 mg, six in the CVT-301 84 mg, and four in the placebo group did not receive any dose of the study medication and were excluded from the intention-to-treat population (339 patients; figure 2). The last patient completed the trial on Dec 6, 2016. The total patient population had a mean Parkinson's disease duration of 8·3 years (SD 4·4) and had, on average, 3·5 off periods per day, despite an average daily levodopa intake of 828 mg. The average daily off time of these patients was 5·5 h, including the early morning off period. Most patients were receiving one or more adjunctive medication for Parkinson's disease. Other baseline characteristics of the study population are shown in table 1.

The primary efficacy measure was change in UPDRS motor score from predose to 30 min postdose (table 2). The least-squares (LS) mean change from predose was −5·91 (SE 1·50; 95% CI −8·86 to −2·96) for the placebo group (n=112) and −9·83 (1·51; −12·79 to −6·87) for the CVT-301 84 mg group (n=114). The LS mean difference between the 84 mg dose and placebo was −3·92 (−6·84 to −1·00; p=0·0088). Secondary endpoints, also assessed at 12 weeks, investigated additional outcomes with CVT-301 versus placebo (table 2). Because the primary endpoint was statistically significant, we proceeded to the next step of testing of the secondary endpoint treatment comparisons. The difference in percentage of patients who, at the 12-week assessment, had and maintained an on response through 60 min (56 [58%] of 97 patients who had measurements at week 12 in the CVT-301 84 mg group *vs* 35 [36%] of 97 in the placebo group) was also statistically significant (p=0·0027; figure 3). Because the hierarchical sequence did not reach statistical significance at step 3 (change in UPDRS motor score from predose to 20 min postdose; p=0·062), subsequent secondary analyses were ineligible for being declared statistically significant.

Although not designated statistically significant because of the hierarchical structure of the study, additional analyses included improvements in PGI-C rating scores (step 4), which revealed that, at week 12, a larger proportion of patients in the CVT-301 84 mg group reported improvement (70 [71%] of 98) compared with the placebo group (45 [46%] of 97, with a nominal p<0·001). Regarding UPDRS motor score assessments at

10 min postdose (step 5) compared with predose values, patients in the CVT-301 84 mg group showed a greater reduction than those in the placebo group (LS mean change –6·45 in CVT-301 84 mg *vs* –4·18 in placebo; nominal p=0·046). The decrease in total daily off time from baseline to week 12 (step 6), as recorded in the patients' home diaries, was similar in the CVT-301 84 mg and placebo groups (LS mean change of –0·47 h in CVT-301 84 mg and –0·48 h in placebo).

At the 12-week visit, the decrease in UPDRS motor scores at each timepoint (ie, 10, 20, 30, and 60 min) was greater for both doses of CVT-301 than for placebo, although only significantly for the 84 mg dose at 30 min (figure 4). Additionally, the change from predose in the average UPDRS motor scores combining all time-points postdose (ie, from 10 to 60 min) showed greater improvement for both the 84 mg (LS mean change –8·97) and 60 mg (–7·91) groups than for the placebo group (–5·57); for these comparisons, the difference between CVT-301 84 mg and placebo was notable (p=0·008), but not the difference between CVT-301 60 mg and placebo (p=0·066). We recognise that this statistical analysis of interaction has low power.[14]

Overall, CVT-301 at 60 mg and 84 mg doses was generally safe and well tolerated. Safety was shown at these doses with exposures up to five times per day. The mean number of doses per day for all treatment groups was approximately two, which remained consistent throughout the 12-week treatment period. Patients were instructed to treat up to five off periods per day, and dosing data reflected the variability of the re-emergence of off periods. For example, in the CVT-301 84 mg group, 57 (50%) of 114 patients took four doses per day at least once, and 30 (26%) patients took five doses per day at least once during the 12-week treatment period.

11 (3%) of 339 patients had 19 serious adverse events (three [3%] of 112 patients in placebo, six [5%] of 113 in CVT-301 60 mg, and two [2%] of 114 in CVT-301 84 mg). Hypotension (one case in CVT-301 60 mg) and atrial fibrillation (one case in CVT-301 84 mg), were the only serious adverse events assessed by investigators to be possibly related to the study drug. There was one reported death (a suicide in a patient receiving CVT-301 60 mg) that was determined to not be related to the study drug. Overall, 49 (44%) of 112 patients in the placebo, 64 (57%) of 113 in the CVT-301 60 mg, and 66 (58%) of 114 in the CVT-301 84 mg group had at least one adverse event during the study (table 3). Reported adverse events with CVT-301 treatment were generally consistent with known adverse events recognised with LD-DCI use, with the addition of pulmonary-related adverse events. The most frequently reported adverse event was cough, which was observed at a lower frequency in the placebo group than in the CVT-301 60 mg and 84 mg groups (table 3). Most adverse events of cough in the CVT-301 treatment groups started within the first 30 days of treatment, and these were generally assessed as mild or moderate in intensity.

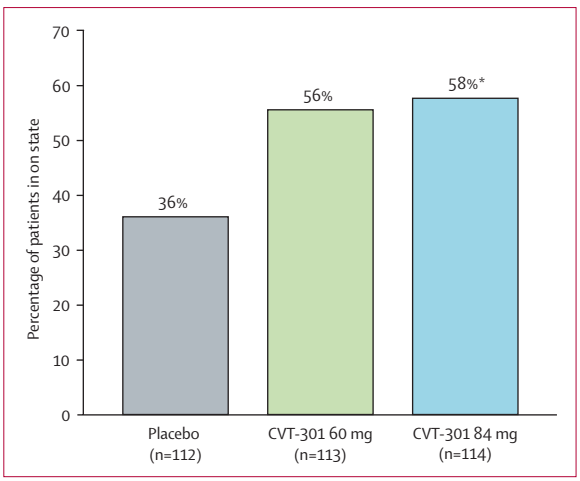

Figure 3: **Proportion of patients in an on state at 60 min postdose at week 12**
*p=0·0027

One patient receiving CVT-301 60 mg reported a severe cough. Three patients (one receiving 60 mg; two receiving 84 mg) had an adverse event of cough that led to study withdrawal. The prevalence of cough was not dose dependent, because about 15% of patients in each CVT-301 group had drug-related cough. In addition to cough, the pulmonary-associated adverse event most frequently reported was throat irritation (table 3). One patient had wheezing associated with CVT-301 60 mg, one had bronchospasm associated with 84 mg, and no adverse events of dyspnoea were reported (table 3).

Overall, 12 (4%) of 339 patients had an adverse event that led to study withdrawal: three (3%) of 112 in the placebo, three (3%) of 113 in the CVT-301 60 mg, and six (5%) of 114 in the CVT-301 84 mg group. Severe adverse events were reported by two (2%) patients in the placebo, seven (6%) in the CVT-301 60 mg, and five (4%) in the CVT-301 84 mg group, and no severe adverse event occurred in more than one patient in any treatment group. Acute pulmonary safety assessments with spirometry done 60 min after inhalation of the first dose of CVT-301 showed no notable differences between placebo and CVT-301 treatment in spirometry parameters (FEV_1, FVC, FEV_1 to FVC ratio). There were nine adverse events of dyskinesia in nine patients (none in placebo, five [4%] in CVT-301 60 mg, and four [3%] in CVT-301 84 mg), although without a dose-proportional pattern. 42% of patients had dyskinesia at baseline, with a similar prevalence among treatment groups. Examiner-rated dyskinesia during the 60-min postdose period in the neurology clinic was more common in the CVT-301 60 mg and 84 mg groups than in the placebo group. Most of the dyskinesia occurrences were mild in severity (but it should be noted that the study excluded patients with pre-existing severe dyskinesias).

Clinical laboratory assessments, vital signs, and ECGs were generally similar among treatment groups and did

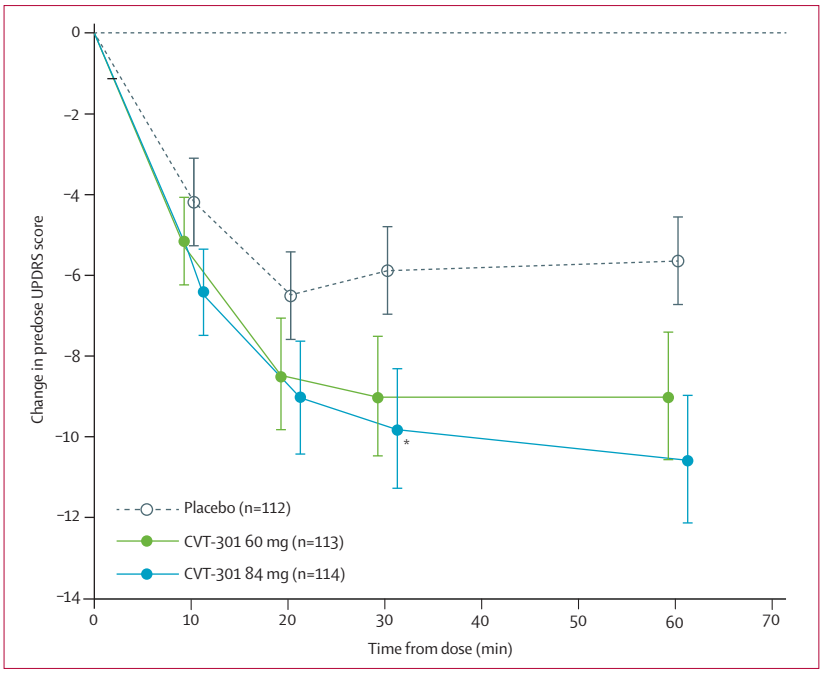

Figure 4: **UPDRS motor score changes from 0 to 60 minutes postdose at week 12**
Data are least-squares mean change and SE. UPDRS=Unified Parkinson's Disease Rating Scale. *Primary efficacy endpoint comparing CVT-301 84 mg versus placebo at 30 min (p=0·0088).

	CVT-301 84 mg (n=114)		CVT-301 60 mg (n=113)		Placebo (n=112)	
	n (%)	Events	n (%)	Events	n (%)	Events
Total	66 (58%)	143	64 (57%)	150	49 (44%)	87
Cough	17 (15%)	18	17 (15%)	20	2 (2%)	2
Upper respiratory tract infection	7 (6%)	7	2 (2%)	2	3 (3%)	3
Nausea	6 (5%)	6	0 (0%)	0	3 (3%)	4
Discoloured sputum	6 (5%)	6	0 (0%)	0	0 (0%)	0
Dyskinesia	4 (4%)	4	5 (4%)	5	0 (0%)	0
Fall	3 (3%)	3	5 (4%)	5	2 (2%)	2
Throat irritation	1 (1%)	1	8 (7%)	8	0 (0%)	0
Dizziness	1 (1%)	1	2 (2%)	2	5 (4%)	5

We report all adverse events that occurred in 4% or more patients in any treatment group. Of these, the following led to study withdrawal: cough (one patient in the CVT-301 60 mg group and two in the 84 mg group), throat irritation (one patient in the CVT-301 60 mg group), and dizziness (one patient in the placebo group).

Table 3: **Adverse events**

not change notably over the duration of the study. Orthostatic hypotension was assessed at the first treatment visit before dosing and at 20 min and 60 min postdose. Orthostatic vital signs were assessed before dosing of the study drug at all subsequent clinic visits and showed similar results between the placebo and CVT-301 84 mg groups, with a numerically, but not significantly, higher incidence of hypotension in the CVT-301 60 mg group. The Epworth Sleepiness Scale revealed no notable worsening in somnolence overall. The Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease revealed no notable evidence for worsening trends in impulsive control disorders across any domain in any treatment group, and there was no indication of compulsive medication use.

Six prespecified sensitivity analyses for the primary endpoint supported the findings of the primary analysis, with one exception. In the analysis that included the addition of region and region-by-treatment interaction in the model (similar to the primary analysis), the 84 mg group had a greater improvement in UPDRS motor score 30 min postdose at week 12 than that of the placebo group (LS mean change –2·61), though the treatment difference was not statistically significant (p=0·094).

Two additional post-hoc analyses support a correlation between the changes observed in UPDRS motor score and clinically meaningful improvements. Patients who responded (that is, achieved and maintained an on state during 60 min postdose) regardless of treatment group had a greater reduction from predose UPDRS motor score at 30 min postdose in all treatment visits. For example, at the week 12 visit, change in UPDRS motor score was –14·6 for responders versus –2·7 for those who did not achieve and maintain an on state during 60 min. Additionally, patients who had improvement per PGI-C assessment had a greater reduction from predose UPDRS motor score at 30 min postdose than those who did not, in all treatment visits. For example, at the week 12 visit, change in UPDRS motor score was –12·1 for patients reporting improvement on PGI-C versus –3·7 for those who did not report improvement.

Discussion

This study supports earlier findings[8] that CVT-301, a levodopa inhalation powder, was generally safe and effective at reducing UPDRS motor score in patients with Parkinson's disease during off periods. In this study, patients receiving the CVT-301 84 mg dose had improvements in UPDRS motor score 30 min postdose at the 12-week assessment. This primary endpoint was further supported with favourable results of patients who had and maintained on responses during 60 min after CVT-301 administration. Although these results were significant on the basis of the hierarchical order established in the statistical plan, the third step in the hierarchy (change in UPDRS motor score from predose to 20 min postdose, with CVT-301 84 mg) was not statistically significant. However, other key secondary endpoints showed nominal p values lower than 0·05, supporting the clinical relevance of the week 12 findings. These include potential improvements on the PGI-C rating scale, a patient-reported secondary endpoint. These findings are promising but require replication in further studies. Additionally, in-clinic observations of parkinsonian motor ratings revealed that patients receiving the 84 mg dose achieved benefits by 10 min after CVT-301 inhalation that lasted through the 60-min assessment. Although patients receiving the

84 mg dose showed greater improvements in UPDRS motor score ratings than those receiving the 60 mg dose, CVT-301 doses did not differ in the number of reported adverse events.

Not all efficacy measures in this study showed superior responses with CVT-301 versus those with placebo. For example, UPDRS motor score change from baseline at 20 min (step 3) was not statistically significant. The Parkinson's disease home diary data also did not show improvements in patients receiving CVT-301. These results, however, were not unexpected for a treatment administered intermittently as needed. The Parkinson's disease diary was completed during three consecutive days before each clinic visit and, therefore, it is possible that the diary period was not representative of the entire inter-visit period. Furthermore, patients reported having 3·5 off periods per day at baseline, including the morning off period, but administered, on average, two doses per day of CVT-301 in the 84 mg cohort during the treatment period. It is possible that, during the study, patients delayed their oral medication after administration of CVT-301, and that the benefit of each CVT-301 administration was neither robust enough nor long enough to show an overall change in daily off-period time. Further inquiries into possible explanations can be explored in subsequent investigations.

Throughout the 12 weeks of the blinded study, CVT-301 was generally well tolerated at both dose levels. The safety profile of CVT-301 was consistent with that of LD-DCI therapy, with the addition of pulmonary-related adverse events (ie, cough). Only 12 study discontinuations were due to adverse events, and overall safety findings were similar for both CVT-301 doses (table 3). With special attention to pulmonary effects, spirometry and carbon monoxide diffusing capacity assessments showed no notable differences between placebo and CVT-301, acutely or throughout the 12-week study, providing evidence for an acceptable pulmonary safety profile. Because CVT-301 is an inhaled drug, cough was of special interest. In both treatment groups, most reported instances of cough were mild and transient after CVT-301 inhalation. Cough was probably an irritant effect related to CVT-301 inhalation and was not evident in the placebo group treated with non-respirable lactose, which generally does not enter the lungs (because of its particle size).

A previous phase 2 study with a single dose of CVT-301 assessed pulmonary function by comparing predose to 3 h postdose findings.[15] Spirometry findings were within normal range for all patients, with no significant spirometry data differences between CVT-301 and placebo over 4 weeks. These findings led to a conclusion that CVT-301 treatment was not associated with acute airflow obstruction.

In this study, the extent of the benefit from CVT-301 treatment might have been limited by the study-based requirement that self-administration could be done no more than five times per day. Although the overall daily off-period incidence averaged 3·5 periods per day at baseline, daily off-period frequency ranged up to 7 periods per day in some patients. The study data do not indicate why patients used the study drug—both CVT-301 and placebo—less often than the five doses per day permitted in the study and less often than the occurrences of off periods. Conceivably, patients might have held back on using the study drug to ensure its subsequent availability later in the day, in anticipation of further off periods. Another possibility is that patients might have refrained from using the study drug soon before their routine ingestion of an oral levodopa dose. Although PGI-C self-ratings of Parkinson's disease improvement favoured CVT-301, these ratings were global assessments summarising weeks of study drug use, rather than an impression of benefit during a specific off period. Another limitation for interpreting efficacy of CVT-301 in controlling off periods was the study requirement that patients could not use the study drug before the first daily oral levodopa dose. Although our study did not assess the potential usefulness of CVT-301 for treating off states upon awakening, another completed trial has investigated this use (NCT02807675); its results are not yet published.

In the clinic visits during the study, patients underwent study drug inhalation shortly after being observed transitioning from on to off state. This decision was made by the examiner at the clinic site, on recognition that one or more parkinsonian symptoms had re-emerged; patients did not need to be in a practically-defined off state, which would require omission of medication for at least 12 h.[16] On this basis, the magnitude of improvement (in UPDRS part 3 score) shown in our study might seem small, even though the dosing resulted in the patient returning to an on state.

Treating off periods with a reliable, well tolerated, and non-invasive treatment would fulfil an important unmet need for many patients with Parkinson's disease. Even with extended-release LD-DCI formulations, adjunctive medications such as dopaminergic agonists and inhibitors of catechol O-methyltransferase and amine oxidase (flavin-containing) B, and closer spacing of immediate-release levodopa doses, patients on long-standing levodopa therapy commonly have delayed and unpredictable onset of anti-parkinsonian effects.[17] In our study, CVT-301 treatment achieved reliable improvements of off periods without an increase in dyskinesia and with an acceptable safety profile. Our findings support continued investigation of CVT-301 for improvement of off periods in patients with Parkinson's disease.

Contributors

PAL, RAH, SHI, and CO contributed to study design. PAL wrote the first draft of the report and revised the text. RAH, RP, SHI, HHF, ML, MS-H, EP, LL-M, CW, MR, AS, RB, and CO contributed to the report. All authors interpreted data and approved the final draft.

Declaration of interests

PAL reports consulting fees from Abide, Acorda Therapeutics, Biogen, Britannia, Cavion, Denali, Intec Pharma, Jazz Pharmaceuticals, Lundbeck, Neurocrine, NeuroDerm, Prexton, Revance, Sage, SynAgile, Titan, and US WorldMeds; lecture fees from Acadia Pharmaceuticals,

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Data sharing

Data will not be publicly available, but requests will be considered on a case-by-case basis. Data sharing proposals and requests will be reviewed by Acorda Therapeutics for approval; the type of data to be made available, the type of analyses permitted, and by which mechanism data will be made available will be determined for each request.

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