# CVN424, a GPR6 inverse agonist, for Parkinson's disease and motor fluctuations: a double-blind, randomized, phase 2 trial

Nicola L. Brice,[a,*] Mark Carlton,[a] David H. Margolin,[a] Martin Bexon,[b] Kim L. Matthews,[a] Lee A. Dawson,[a] Aaron L. Ellenbogen,[c] C. Warren Olanow,[d,e] Jordan Dubow,[d] and Karl Kieburtz[d]

[a]Cerevance, 418 Cambridge Science Park, CB4 0PZ, Cambridge, United Kingdom
[b]Bexon Clinical Consulting LLC, 551 Valley Road #200, Upper Montclair, NJ, 07043, USA
[c]Michigan Institute for Neurological Disorders, Farmington Hills, MI, USA
[d]Clintrex Research Corp, Sarasota, FL, USA
[e]Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA

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## Summary

**Background** CVN424 is a GPR6 inverse agonist that provides selective pharmacological control of the indirect striatopallidal pathway. We assessed the safety and efficacy of CVN424 as an adjunctive treatment to levodopa for reducing OFF-time in individuals with Parkinson's disease (PD) experiencing motor-fluctuations.

**Methods** This was a randomised, double-blind, placebo-controlled study conducted at 21 sites across the United States to evaluate two doses of CVN424 (NCT04191577). Patients with PD (Hoehn and Yahr stages 2–4) who were on a stable dose of levodopa and experiencing ≥2 h of daily OFF-time were randomised (1:1:1) to receive either once-daily CVN424 (50 mg or 150 mg) or placebo for a 28-day treatment period. The primary endpoints were safety and tolerability. The key secondary endpoint was the change from baseline to Day 27 in OFF-time.

**Findings** The study was conducted from December 23, 2019, to October 14, 2021. Out of 198 participants screened, 141 eligible participants were randomised to one of the three treatment groups (n = 47 per group), and 127 participants completed the 28-day treatment period. The most common treatment emergent adverse events (TEAEs) were headache (2% with CVN424 50 mg, 9% with CVN424 150 mg, and 2% with placebo) and nausea (4% with CVN424 50 mg, 6% with CVN424 150 mg and 2% with placebo). No serious treatment-related adverse events were reported. On Day 27, the mean ± standard deviation (SD) change from baseline in daily OFF-time was −1.3 ± 3.0 h in the CVN424 50 mg group, −1.6 ± 2.5 h in the CVN424 150 mg group, and −0.5 ± 2.9 h in the placebo group. The placebo-adjusted LS mean ± standard error (SE) treatment difference was significant for the CVN424 150 mg dose (1.3 ± 0.56 h, [95 CI% −2.41 to −0.19], nominal p = 0.02).

**Interpretation** Treatment with CVN424 was safe and well-tolerated. Despite the short study duration and small sample size, the 150 mg CVN424 dose provided a clinically meaningful reduction in daily OFF-time. This study supports the development of CVN424 for the treatment of PD.

**Funding** Cerevance.



**Keywords:** Parkinson's disease; Motor fluctuations; CVN424; GPR6; Striatum; Indirect pathway

## Introduction

Currently, levodopa and other dopaminergic therapies form the mainstay of symptomatic treatment for Parkinson's disease (PD).[1] Parkinsonian motor symptoms are primarily caused by the progressive loss of dopaminergic neurons in the substantia nigra *pars compacta*, which innervate medium spiny neurons (MSNs) of the striatum.[2] Therefore, rational approaches to treating motor complications have primarily focused on manipulation of dopaminergic tone by adjusting the levodopa dose, or adding dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, or monoamine oxidase

*Corresponding author. Cerevance, 418 Cambridge Science Park, Cambridge, CB4 0PZ, UK.
*E-mail addresses:* info@cerevance.com (N.L. Brice), mark.carlton@cerevance.com (M. Carlton), david.h.margolin@gmail.com (D.H. Margolin), martin.bexon@bexonclinical.com (M. Bexon), k.matthews@sitala.com (K.L. Matthews), lee.dawson@cerevance.com (L.A. Dawson), aellenbogen@comcast.net (A.L. Ellenbogen), warren.olanow@clintrex.com (C.W. Olanow), jordan.debow@clintrex.com (J. Dubow), kkieburtz@clintrex.com (K. Kieburtz).

## Research in context

### Evidence before this study

We searched PubMed and ClinicalTrials.gov for reports on the management of levodopa-induced motor fluctuations published in English between database inception and April 26, 2024. We used the search terms *"levodopa, adjunct, motor fluctuations, motor complications."* Previous studies with dopaminergic-based adjunctive therapies reported benefits for reducing OFF-time (periods of poor motor control) by 0.8 to 1.0 h. However, most dopaminergic adjunct therapies increase the risk of dyskinesia. CVN424 is a novel, highly potent, selective, small-molecule, inverse agonist of the GPR6 G-protein coupled receptor that has a highly enriched expression in the dopamine D2 receptor expressing medium spiny neurons that comprise the indirect striatopallidal pathway. Preclinical studies demonstrate that CVN424 is effective in reversing locomotor deficits in animal models of PD, and a phase 1 study showed that repeated doses of up to 150 mg per day are safe and well-tolerated.

### Added value of this study

This study marks the initial demonstration that modulating GPR6 can improve motor features of PD without inducing clinically meaningful adverse effects or dyskinesia. Despite its small size and duration, this study demonstrated that CVN424 reduced OFF-time to a similar extent as traditional dopaminergic adjunct therapies. Improvements across secondary and exploratory endpoints suggest that CVN424 may have benefits on both the motor and non-motor clinical manifestations of PD.

### Implications of all the available evidence

In this phase 2 study, once-daily treatment with CVN424 was safe and well-tolerated. The CVN424 150 mg dose showed a similar magnitude of efficacy as the traditional dopaminergic adjunct therapies, but without the dopaminergic adverse events that can limit their effectiveness. These data suggest that modulating GPR6 could offer a promising strategy for the management of PD, justifying advancement to a phase 3 clinical programme.

B (MAO-B) inhibitors to the treatment regimen. While dopamine replacement strategies can adequately address the motor symptoms in the early stages of PD, they are often associated with adverse events (AEs) such as somnolence, nausea, dizziness and orthostatic hypotension. Moreover, with sustained and higher doses of levodopa, the majority of patients eventually develop motor complications—such as motor fluctuations and dyskinesia[3–5]—which can lead to functional impairment and reduce the individual's quality of life.[6,7] The only nondopaminergic approaches are the multimodal drug amantadine and the adenosine $A_{2A}$ receptor antagonist istradefylline.[8] However, the efficacy and tolerability of all these approaches is limited, and a proportion of patients will progress to advanced invasive therapies.[9] There remains a need for new oral approaches that provide sustained benefits while minimising motor complications and other adverse effects.

CVN424 is a potent and selective inverse agonist of G-protein coupled receptor 6 (GPR6), an orphan receptor that is predominantly expressed in the dopamine D2 receptor expressing MSNs that project from the striatum to the external pallidum and comprise the indirect pathway.[10] Expression of GPR6 in other cell types, brain regions, and peripheral tissues is low or absent, making it an attractive nondopaminergic target for the treatment of PD.[11,12] As an inverse agonist of GPR6, CVN424 decreases intracellular cyclic adenosine monophosphate (cAMP),[9] supplementing or substituting dopamine's inhibitory effect on D2 receptors, and potentially reducing the pathological hyperactivity of the D2 receptor expressing MSNs in PD and the risk of dyskinesia. Preclinical data has shown that CVN424, achieves near maximal striatal receptor occupancy and is effective in reversing locomotor deficits in the 6 hydroxydopamine (6-OHDA) lesion rat model of PD.[11,13] Data from phase 1 single- and multiple-ascending dose studies show that CVN424 is generally safe and well tolerated in healthy adults, with relatively linear dose-dependent increases in exposure after both single or multiple administrations.[14]

The main objectives of this phase 2 study were to assess the safety and tolerability of two doses of CVN424 compared to placebo as an adjunctive therapy to levodopa in people with PD experiencing motor fluctuations. A secondary objective was to assess the efficacy of CVN424 for reducing daily OFF-time. We also aimed to characterise the plasma pharmacokinetics of multiple-doses of CVN424 in a PD population.

## Methods

### Study design, participants and ethics

We conducted a randomised, double-blind, placebo-controlled study to evaluate two doses (50 mg or 150 mg) of oral CVN424 in people with PD experiencing motor fluctuations. The study was conducted at 21 movement disorder clinics across the USA in accordance with the Declaration of Helsinki and approved by the USA Food and Drug Administration (FDA). Study protocols and amendments were approved by the Institutional Review Boards at each site and all participants provided written informed consent.

Eligible participants were men and women (determined by medical records) aged 30–80 years with a diagnosis of PD[15] at Hoehn and Yahr stages 2–4 (during

ON periods). They were on a stable dosage of levodopa and other antiparkinsonian medications for at least 30 days prior to this study and maintained for the duration of the study. Eligible participants experienced an average of at least 2 h of OFF-time over 2 days during the initial evaluation, as recorded in the self-completed Hauser diary.[16] Participants were excluded if they demonstrated poor diary compliance during the screening period, had atypical parkinsonism, or severe motor fluctuations that the Investigator considered likely to interfere with study participation or assessments. Participants were also ineligible if they had a history of deep brain stimulation.

### Randomisation and masking

Eligible participants were randomly assigned in a 1:1:1 ratio (blocks of 3) using an interactive response system (Bioclinica) to receive a once-daily dose of CVN424 (50 mg or 150 mg) or matching placebo. The study drug was provided as an oral suspension in amber coloured bottles to mask the appearance of the liquid. All participants, investigators, trial team, and sponsors were blinded to treatment throughout the study.

### Procedures

Following a screening period of up to 28 days (during which participants received standardised instructions on how to complete the Hauser diary), baseline efficacy and safety assessments were performed prior to randomisation and administration of study medication. On Day 1 of dosing, participants received their study medication in the morning and vital signs were monitored for 3 h post-dose. Participants randomised to CVN424 150 mg/day received 50 mg/day for the first week and increased to 150 mg/day on Day 8. Participants visited the clinic once a week on Days 1, 8, 15, 22, 27, and 35, when weekly kits of the study drug were supplied, and empty bottles returned.

Blood samples for pharmacokinetic analysis of CVN424 plasma concentrations were collected pre-dose and 3 h post-dose on Days 1 and 8; pre-dose and 1-, 1.5-, 2-, 4-, and 6-h post-dose on Day 22; and post-dose on Days 15 and 27 (time not specified).

### Outcomes

The primary safety endpoint was the percentage of participants with treatment emergent adverse events (TEAEs) related to study drug during the study period. Additionally, physical examinations, vital sign assessments (including oral temperature, respiration, heart rate, and blood pressure), 12-lead electrocardiograms (ECGs), and laboratory studies (haematology, serum chemistry, urinalysis, and endocrine) were conducted during clinic visits. Participants completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) and Beck Depression Inventory (BDI) at randomisation and on Day 27 or at the early termination visit. The primary tolerability endpoint was the proportion of participants completing the trial.

Plasma concentrations of CVN424 were evaluated using a validated high-performance liquid chromatography method with tandem mass spectrometry.[14]

The key efficacy endpoint was the change from baseline to Day 27 in the average daily OFF-time, as recorded over 2 days in the Hauser diary. Exploratory diary-based outcomes included the 2-day average total daily ON time, ON time without troublesome dyskinesia, and ON time with troublesome dyskinesia on Days 15 and 27. Responders were defined as greater than 30% improvement in OFF time. Other exploratory efficacy endpoints included the Clinical Global Impression- (CGI) and the Patient Global Impression- (PGI) Severity and Change scales, and the change from baseline to Days 15, 27, and 35 in the Unified Parkinson's Disease Rating Scale (UPDRS)[17] Parts 1, 2, 3, and 4, and the Epworth Sleepiness Scale (ESS).[18]

### Statistical analysis

The sample size of 45 participants per treatment arm (total N = 135) was sufficient for the preliminary evaluation of CVN424's safety, tolerability, and efficacy. The sample size and study sites were increased during the study from total participants n = 66 to ensure more robust safety and efficacy analyses. The study had a statistical power of 90% to detect at least one instance of any TEAE with an expected incidence rate of 0.10 per participant exposed to a given dosage of CVN424. If the true effect of both doses was zero, the study had an 80% probability of stating that neither dosage of CVN424 exhibited significantly better efficacy over placebo for reducing OFF-time, based on the 1-tailed $p < 0.10$ criterion, with a 20% allowance for non-evaluable participants (e.g., loss to follow-up, incomplete data) and assuming a standard deviation (SD) of 3 h for the change in OFF-time from baseline to Day 27. When the true effect of a dosage was a reduction in the average OFF-time of at least 1.5 h, the study had an 80% probability of declaring that the dosage of CVN424 was significant based on the 1-tailed $p < 0.10$ criterion. By this construction, the study had an 80% probability to detect whether CVN424 did not reduce OFF-time and an 80% probability to detect whether CVN424 at one or both dosages reduced OFF-time by at least 1.5 h.

Safety and efficacy endpoints were analysed for all randomised participants who received ≥1 dose of study drug. Pharmacokinetic assessments were analysed for all randomised participants who received ≥1 dose of study drug and who had ≥1 measurable plasma concentration. TEAEs and abnormal results for clinical laboratory evaluations were summarised by treatment group. The plasma pharmacokinetics of CVN424 was characterised using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.).

The key efficacy endpoint (reduction in OFF-time) was analysed using a Bayesian mixed model repeated measures (MMRM) with fixed terms for treatment, visit, treatment × visit interaction, and baseline measurement with participant-level unstructured covariance among repeated measurements. Responders were analysed and defined as participants with ≥30% decrease in OFF-time. The number and percentage of responders were summarised by visit and overall, including responders at only Day 15, only Day 27, and at both Day 15 and Day 27. Between group differences in the number of responders, as well as CGI and PGI parameters, were analysed using the Proportional Odds Model with the Generalised Estimating Equations (GEE) method. Other exploratory endpoints were analysed using the same MMRM approach applied to the key efficacy endpoint.

A *post-hoc* supplementary analysis was performed to conform to the FDA standardised analysis for the Hauser diary, which normalises the data to a 16-h period of wakefulness and excludes incomplete diaries (fewer than 44 of 48 entries completed in a day). In this analysis, participants were also excluded if they had <3 h of OFF-time at baseline as most clinical registrational studies of PD fluctuations typically require participants to have ≥2.5–3 h of OFF-time at baseline.[19,20]

The study is registered on ClinicalTrials.gov, NCT04191577 and is complete.

### Role of the funding source

The funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The authors had full access to the data and made the decision to submit for publication.

## Results

The study was conducted to completion between December 2019 and August 2021. A total of 198 individuals underwent screening, of whom 141 (71%) were enrolled and randomised (n = 47 per group), and 127 completed the study. Five randomised participants did not receive study treatment and three participants (6%) from each group discontinued early (Fig. 1). Baseline characteristics were similar across groups except for sex, with a higher proportion of females in the CVN424 150 mg group compared to the other groups (Table 1).

Three participants (6%) from each group discontinued early, including one participant each from the placebo and CVN424 50 mg groups who discontinued due to physician decision. Seven participants (5%) discontinued due to TEAE, with four withdrawing during the first eight days of treatment (i.e., when participants in the CVN424 150 mg group were still receiving 50 mg as part of their dose escalation). Reasons for discontinuation included one in the placebo group due to a behaviour disorder, one in the 50 mg group due to nausea, and one participant in the 150 mg group due to nausea, dizziness, headache, and tremor. A participant in the CVN424 150 mg group died due to a serious TEAE of cardiac arrest and seizure on Day 2. The event was considered not treatment-related, due to the participant's medical history that included hyperlipidaemia,

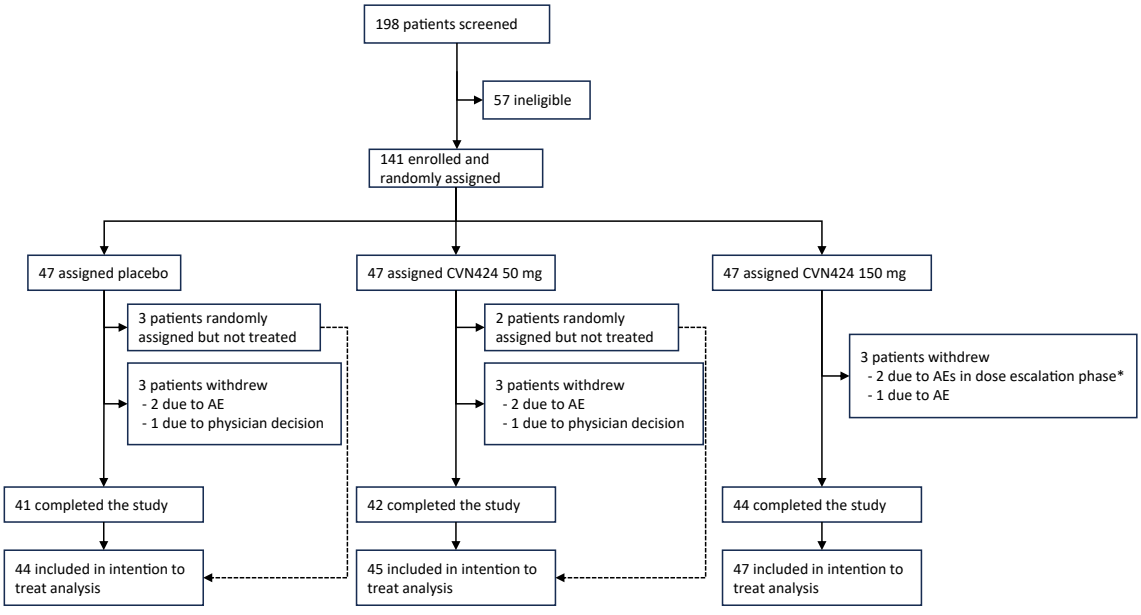


***Fig. 1:*** Trial profile. *Participants received CVN424 50 mg during dose escalation; one participant had an unrelated cardiac arrest and subsequent epileptic seizure on Day 2 and died on Day 7.

coronary artery disease, angina, and two prior cardiac stents. Three additional participants discontinued due to a TEAE after Day 8. Reasons for discontinuation included one in the placebo group due to angina pectoris, one in the 50 mg group due to anxiety, and one in the CVN424 150 mg group due to hallucinations and nightmares on Day 15.

There was a higher incidence of TEAEs in participants taking 50 mg and 150 mg CVN424 than in the placebo group (27% and 36% versus 23%, respectively) (Table 2). Most TEAEs were grade one or two (mild or moderate) in severity. The most common TEAEs by preferred terms were headache and nausea, with headache reported in four (9%) participants in the 150 mg group and one each in the placebo (2%) and 50 mg (2%) groups. Nausea was reported in three participants in the 150 mg group (6%), two participants in the 50 mg group (4%), and one participant in the placebo group (2%). Dyskinesia, as a TEAE, was reported in only one participant in the 150 mg group prior to dose escalation (2%) and two participants reported hallucinations. One of these participants was in the placebo group (2%) and one in the 150 mg group (2%). The overall incidence of treatment-related TEAEs (primary safety endpoint) was low. Eight participants (17%) reported a total of 12 treatment-related events with low dose CVN424, nine (19%) reported a total of 19 treatment-related events with high dose CVN424, and four (9%) reporting a total of four treatment-related events with placebo. No treatment-related serious TEAEs were reported. There were no notable changes in laboratory parameters, physical examinations, ECGs, and BDI scores during the study. There were no clinically relevant changes in blood pressure or pulse rate.

A summary of the pharmacokinetic findings is presented in Appendix 1 (p2). Exposure to CVN424 increased with dose level (Fig. 2). Based on mean $C_{max}$, $C_{min}$, and $AUC_6$, the 3-fold increase in CVN424 dose from 50 mg to 150 mg resulted in a 2.6-fold increase in exposure.

The mean ± SD change from baseline to final visit in the average daily hours of OFF-time was –1.3 ± 3.0 h in the CVN424 50 mg group, –1.6 ± 2.5 h in the CVN424 150 mg group, and –0.5 ± 2.9 h in the placebo group at Day 27. The study met its key efficacy endpoint with the higher CVN424 150 mg dose, which demonstrated a significant least squares (LS) mean ± SE placebo-adjusted improvement in OFF-time of 1.3 ± 0.56 h [95 CI% –2.41 to –0.19] (p = 0.02) (Fig. 3a). The treatment difference was not significant for the CVN424 50 mg dose versus placebo. (Supplementary subgroup analysis (data normalised to a 16 h waking day) of the 105 participants with > 3hr OFF time and at least one post-baseline assessment), confirmed the findings of the primary analysis. In this subpopulation, treatment with CVN424 150 mg group reduced OFF-time by 1.78 h (nominal p = 0.0045) compared to placebo (Fig. 3b). At Day 27, 37% and 57% of participants in the 50 mg and 150 mg CVN424 groups, respectively, achieved the definition of responder compared to 33% in the placebo

| Baseline demographics | Placebo (N = 44) | CVN424 50 mg (N = 45) | CVN424 150 mg (N = 47) |
|---|---|---|---|
| Age, years | 67.0 ± 7.1 | 63.0 ± 7.7 | 65.6 ± 9.1 |
| Sex | | | |
| Male | 34 (77%) | 33 (73%) | 27 (57%) |
| Female | 10 (23%) | 12 (27%) | 20 (43%) |
| Body mass index (kg/m$^2$) | 28.18 ± 4.3 | 27.45 ± 4.7 | 28.27 ± 4.3 |
| Levodopa dosage, mg | 538 ± 258 | 547 ± 429 | 580 ± 360 |
| Average daily OFF-time at baseline, h/day | 5.4 ± 2.1 | 5.3 ± 2.4 | 5.1 ± 2.1 |
| Average UPDRS II score at baseline | 11.9 ± 4.9 | 12.4 ± 5.4 | 12.4 ± 5.5 |
| Average UPDRS III score at baseline | 23.7 ± 9.2 | 22.8 ± 11.7 | 22.8 ± 10.4 |
| **Concomitant PD medication** | | | |
| Levodopa/carbidopa | 44 (100%) | 47 (100%) | 45 (100%) |
| Dopamine agonists | 21 (48%) | 18 (38%) | 18 (40%) |
| MAO-B inhibitors | 9 (21%) | 10 (21%) | 12 (27%) |
| Amantadine | 3 (7%) | 10 (21%) | 10 (22%) |
| Istradefylline | 0 | 0 | 1 (2%) |

Data are mean (SD) or n (%), unless otherwise indicated. MAO-B = monoamine oxidase type B.

*Table 1:* **Demographic and clinical characteristics (Safety set).**

| | Placebo N = 44 | CVN424 50 mg N = 45 | CVN424 150 mg N = 47 |
|---|---|---|---|
| **Overall summary** | | | |
| Any TEAE | 10 (23%) | 12 (27%) | 17 (36%) |
| Serious TEAE | 0 | 0 | 1 (2%) |
| Death | 0 | 0 | 1 (2%) |
| TEAE leading to discontinuation | 2 (5%) | 2 (5%) | 3 (7%)[a] |
| **TEAEs reported for ≥2 participants in any group** | | | |
| Headache | 1 (2%) | 1 (2%) | 4 (9%) |
| Nausea | 1 (2%) | 2 (4%) | 3 (6%) |
| Constipation | 1 (2%) | 0 | 2 (4%) |
| Dizziness | 1 (2%) | 0 | 2 (4%) |
| Fatigue | 2 (5%) | 0 | 0 |
| COVID-19 | 2 (5%) | 1 (2%) | 0 |
| **Treatment-related TEAEs (primary safety objective)** | | | |
| Treatment-related TEAE | 4 (9%) | 8 (18%) | 9 (19%) |
| Nausea | 0 | 2 (4%) | 2 (4%) |
| Headache | 0 | 0 | 2 (4%) |
| Vomiting | 0 | 0 | 2 (4%) |
| Tachycardia | 0 | 2 (4%) | 0 |
| Tremor | 0 | 0 | 1 (2%) |

Data are n (%). [a]Two participants in the CVN424 150 mg group (including one death) discontinued due to TEAEs while receiving a dose of 50 mg. Adverse events defined by MedDRA (v. 24.0).

*Table 2:* **Treatment emergent adverse events (Safety set).**

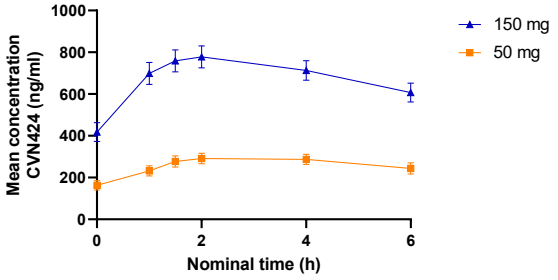


*Fig. 2:* CVN424 plasma concentration-time plots by dose (PK analysis set). Data shown are mean (±SE) concentrations.

group. The difference between CVN424 150 mg versus placebo was statistically significant (p = 0.031).

Results for the exploratory efficacy results are shown in Appendix 1, p3. Decreases in OFF-time were accompanied by trends towards increased total daily ON time (LS mean ± SE placebo-adjusted improvement 1.09 ± 0.59 [95% CI −0.08 to 2.26] p = 0.067) and ON time without troublesome dyskinesia (0.67 ± 0.61 [95% CI −0.54 to 1.89] p = 0.27). at 150 mg dose. Treatment with CVN424 did not demonstrate significant benefit on CGI, PGI or UPDRS (Parts 1–4) scores at either dose or at any time point. At Day 15, participants in the CVN424 150 mg group demonstrated a significantly improved ESS score of −1.35 ± 0.68 compared to placebo (nominal p = 0.049). While the difference versus placebo at Day 27 was not significant, a similar trend was observed (−1.0 ± 0.64; nominal p = 0.12). Planned sub-group analysis included comparing participants who were, or were not, taking a dopamine agonist to placebo. In this analysis participants not taking dopamine agonists showed a significant LS mean improvement in OFF time in the 150 mg group of −2.18 ± 0.82 h [95% CI −3.8 to −0.55] (p = 0.0096), while those on dopamine agonists showed a smaller improvement. A trend to improvement was seen in the 50 mg group Appendix 1, p4.

## Discussion

In this double-blind, randomised study, treatment over a 28-days period with the GPR6 inverse agonist, CVN424, was safe and well-tolerated when administered as an adjunctive therapy to levodopa and other dopaminergic drugs. Additionally, the 150 mg dose was superior to placebo for reducing OFF-time in PD participants with levodopa-related motor fluctuations (p = 0.02). Consistent with the phase 1 study, exposure to CVN424 increased with dose.[14]

There were no treatment-related serious TEAEs reported with CVN424 treatment. The absence of increase in the classic dopaminergic TEAEs associated with current dopamine replacement therapies is consistent with the hypothesis that CVN424 specifically targets the 'indirect' striatopallidal pathway without affecting dopaminergic tone in other brain regions. For example, the lack of dyskinesia reported as a TEAE with CVN424 is consistent with the lack of effect on the dopamine D1 receptor expressing direct pathway as overstimulation of this pathway is believed to play a primary role in the development of dyskinesia.[21] Likewise, the relatively low prevalence of nausea and vomiting compared to traditional dopaminergic agents is consistent with the lack of GPR6 expression in the periphery and chemoreceptor trigger zone (area postrema) of the medulla oblongata.[22] Treatment with CVN424 was generally well tolerated with 94% of participants continuing treatment. Most discontinuations due to AEs occurred early, within the first week of treatment. The only observed serious AE, which was fatal, also occurred early in the study (following two doses of CVN424 50 mg) but was not considered treatment-related due to the participant's history of significant cardiac risk factors. There were no observed changes or trends in safety laboratory values and ECGs. Of note, there was no evidence of clinically significant changes in blood pressure, heart rate, or ECG this study, nor in the prior phase 1 study.[14]

This study is the first demonstration that modulating GPR6 can improve the motor features of PD. GPR6 is a

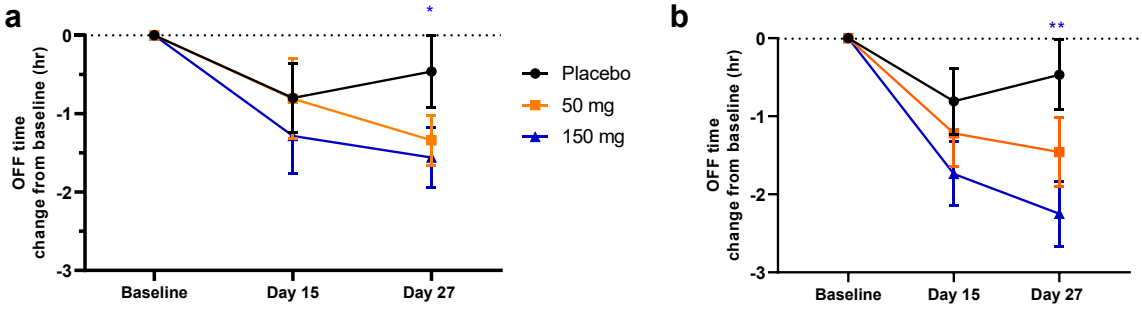


***Fig. 3:* Mean (SE) change from baseline in daily OFF time by visit (a) Efficacy population (b) FDA standardised analysis (≥3 h OFF time at baseline) population**. The standard FDA analysis included patients with ≥3 h of OFF-time at baseline and normalises Hauser diary data to a 16-h period of wakefulness and excludes incomplete diaries (fewer than 44 of 48 entries completed in a day). Data shown are LS mean (±SE). Blue stars correspond to 150 mg group * p < 0.05; **p < 0.01 compared to vehicle (MMRM).

constitutively active G-protein coupled receptor, which increases adenylate cyclase activity, thereby continuously activating the indirect striatopallidal pathway.[23] CVN424 suppresses this constitutive activity, reducing cellular cAMP levels[11,13] and attenuating the pathologic hyperactivity of the indirect pathway seen in PD. Despite the short duration of treatment and the small sample size, the magnitude of OFF-time improvement observed in the CVN424 150 mg group (1.3-h improvement in OFF-time compared to placebo) is clinically relevant[24] and is similar to that achieved by oral dopaminergic therapies, including MAO-B inhibitors, COMT inhibitors, and dopamine receptor agonists.[25] The supplementary analyses replicating the conditions typically used in other studies of interventions for motor fluctuations reinforced the observed magnitude of effect. The decrease in OFF-time was accompanied by a non-significant increase of 0.7-h in ON time without troublesome dyskinesia for the CVN424 150 mg group without any significant worsening of ON time with troublesome dyskinesia.

Excessive daytime sleepiness is a common problem in PD and is frequently exacerbated by treatment.[26] While somnolence is often a dose-related AE associated with dopamine agonists,[27] participants on CVN424 demonstrated a trend towards improvement in ESS scores, rather than a lack of worsening. This may reflect effects on the D2 receptor-expressing neurones of the ventral striatum, which are involved in the pathophysiology of apathy, fatigue, and cognitive deficits, and have also been associated with excessive daytime sleepiness in PD.[28–30] It will be of interest to consider the impact of CVN424 on these non-motor manifestations of PD in future studies.

We acknowledge limitations of this proof-of-concept study. The primary objectives were safety and tolerability and efficacy in reducing OFF time was assessed as a secondary outcome. While the exploratory CGI and PGI results did not reveal any changes, this finding may be due to the study's short duration (28 days) and small sample size. Further, the study recruited participants with at least 2 h of OFF-time, while most other studies patients with PD experiencing motor fluctuations utilise a population with a minimum of 2.5–3 h of OFF time at baseline. Although restricting the population to try and match the conditions of other studies improved the magnitude of treatment effect, the supplementary analysis was *post-hoc* and should be interpreted with due caution. Finally, this study was conducted during the COVID-19 pandemic and multiple participants had delayed visits due to isolation, lockdown restrictions, and/or potential exposure. A further prospective study with a larger sample size and longer duration is required to conduct a comprehensive assessment CVN424's safety in PD patients and to determine the durability of its effect in PD.

In summary, CVN424 appears to be generally safe and well tolerated. Efficacy in reducing OFF-time was demonstrated despite short treatment duration and small sample size, supporting the utility of GPR6 as a nondopaminergic therapeutic target in PD. Furthermore, improvements observed across exploratory endpoints suggest that CVN424 may offer benefits for the motor aspects of PD, and shows encouraging results for non-motor clinical manifestations of PD such as excessive daytime sleepiness. A multicentre, 12-week, placebo-controlled clinical trial of CVN424 (150 mg) is underway (NCT06006247) to evaluate its potential efficacy as a monotherapy in patients with early, untreated PD.

#### Contributors

NLB, MC, DHM, KLM, LAD, CWO, JD, MB and KK contributed to the study design and conducting the study or data analysis. ALE was a study investigator. NLB, MC and KLM and KK had access to the original data, verified the data, and NLB and KK contributed equally to the first draft; all other authors participated in the critical revision of the manuscript. All authors had full access to all the data, were involved data interpretation and had final responsibility for the decision to submit for publication.

#### Data sharing statement

Cerevance will share deidentified data from this study with qualified researchers who provide a valid research question and sign a data access agreement. Address proposals to info@cerevance.com.

#### Declaration of interests

NLB, MC, DHM, KLM, and LAD are employed by Cerevance. Martin Bexon reports consultancy to Cerevance. ALE reports honoraria and consulting fees from AbbVie, Acadia, Acorda, Adamas, Affiris, Allergan, Arbor, Biohaven, BioVie, Cerevel, Ipsen, Mitsubishi Tanabe Pharma America, NeuroDerm, Praxis, Revance, Supernus, Teva, US WorldMeds, and XW Labs. C. Warren Olanow has equity interest in Clintrex and has served as an expert witness in the paraquat litigation. JD is an adviser to Cerevance via Clintrex, and the owner of Dubow CMO Consulting, LLC. KK reports equity interest in Clintrex and Hoover Brown, patents for information management, and participation in safety monitoring boards for Roche, Lilly, and Janssen.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102882.

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