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Improvement in Quality of Life and Non-Motor Symptoms Associated With OFF Episodes in People With Parkinson's Disease Treated With Inhaled Levodopa

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ABSTRACT

Background: CVT-301 (Inbrija) has demonstrated its effectiveness in treating OFF periods in people with Parkinson's disease (PwP). However, its effect on non-motor symptoms (NMS) and quality of life has not been researched yet. Our aim was to analyze the change observed in health-related quality of life (HRQoL) and, as a secondary exploratory analysis, NMS associated with OFF episodes in PwP treated with CVT-301.

Methods: INLEVO-LIFE PD (an open-label study of the effect of INhaled LEVOdopa on quality of LIFE and non-motor symptoms in Parkinson's Disease) is a prospective open-label study conducted in five centers in Spain. The change from baseline (V0) to the end of the observational period (12 ± 2 weeks) (V12w) in the 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) total score was the primary efficacy measure.

Results: Forty PD patients (age 62.3 ± 9.2 years; 55% males) were included between March/2024 and November/2025. At 12 weeks, 34 patients were using CVT-301 and completed the follow-up (85%). The PDQ39 total score decreased from 43.6 ± 24.2 at V0 to 31.4 ± 20.6 at V12w ($p < 0.0001$). A significant decrease was observed in the mean score of 4 domains of the PDQ39. NMS burden was reduced at v12w from the OFF state to 30, 60, and 90 min after using CVT-301 ($p < 0.0001$). Mean daily OFF time decreased by 1.6 ± 1.9 h ($p < 0.0001$). Adverse events related to CVT-301 were reported in 35% of the patients.

Conclusion: HRQoL and NMS associated with OFF episodes improved in PwP after 12 weeks using CVT-301.

Abbreviations: ADL, activities of daily living; ADLS, Schwab and England Activities of Daily Living Scale; CGI-I, Clinical Global Impression Scale Improvement; CGI-S, Clinical Global Impression Scale Severity; EUROHIS-QOL8, EUROHIS-QOL 8-item index; GQoL, global quality of life; HRQoL, health-related quality of life; LEDD, levodopa equivalent daily dose; MDS, Movement Disorder Society; NMF, non-motor fluctuations; NMS, non-motor symptoms; PD, Parkinson's disease; PDQ-39, the 39-item Parkinson's Disease Quality of Life Questionnaire; PwP, people with Parkinson's disease; QoL, quality of life; RCTs, randomized controlled trials; UPDRS, Unified Parkinson's Disease Rating Scale.

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1 | Introduction

On-demand therapies in Parkinson's disease (PD) are pharmacologic interventions specifically designed to provide rapid relief from acute OFF episodes—periods when motor and non-motor symptoms (NMS) re-emerge due to insufficient dopaminergic stimulation, often occurring unpredictably or between scheduled doses of levodopa [1–3]. One of the currently available on-demand therapies is CVT-301 (Inbrija), a novel inhalation powder consisting of levodopa and administered by oral inhalation using a passive breath-actuated delivery system [4]. This drug has undergone extensive clinical trials and was approved by the Food and Drug Administration in 2018 and by the European Medicines Agency in 2019 for the intermittent treatment of OFF periods in patients with PD [5]. In several randomized controlled trials (RCTs) with about 900 PD patients treated, CVT-301 has consistently demonstrated its effectiveness in treating OFF periods and improving motor symptoms in people with PD (PwP) [6–8]. Importantly, CVT-301 provides a faster therapeutic onset in patients with PD because it is rapidly absorbed into the lung epithelium and directly transported to the central nervous system [9], and it has been demonstrated to be safe and well tolerated as well [10]. However, the effect of CVT-301 on NMS associated with OFF episodes and patients' quality of life (QoL) has not been researched yet. Since CVT-301 is a symptomatic treatment for PD, the goal of its use is to improve symptoms in order to improve the patients' QoL, which is a key aspect to evaluate. Furthermore, it is interesting to know if CVT-301 can improve the NMS associated with OFF episodes, given that non-motor fluctuations (NMF) could have a greater impact on the patients' QoL than the motor fluctuations themselves [11]. Finally, the effect of CVT-301 [6–8] has been demonstrated for 60 min, but it is not known if it could have a longer-lasting effect.

In this context, we developed the INLEVO-LIFE PD study (An open-label study of the effect of INhaled LEVOdopa on quality of LIFE in Parkinson's Disease). Our hypothesis was that PD patients' QoL could improve with the use of CVT-301 due to a reduction in OFF time and severity of OFF episodes (motor symptoms and NMS). The primary objective was to analyze the change observed in health-related quality of life (HRQoL) in PwP treated with CVT-301. Secondary aims were to analyze the change observed in global quality of life (GQoL), autonomy for activities of daily living (ADL), OFF time, NMS, and clinical global impression of change after 3 months of using it, as well as its safety and tolerability. As an exploratory analysis, the change observed in NMS burden added to motor state after 30, 60, and 90 min of CVT-301 administration was also analyzed.

2 | Materials and Methods

The INLEVO-LIFE PD study is a mono-country (Spain), multicenter, observational (phase IV), prospective, open-label, follow-up study. Five neurologist experts on PD from 5 centers in Spain (CHUAC; Complejo Hospitalario de Cartagena; CHUO; CHOP; Hospital de Povisa) participated in the recruitment and evaluation of participants. A total of 40 consecutive patients diagnosed with PD according to the MDS (Movement Disorder Society) clinical diagnostic criteria [12] without dementia [13] were expected to be included in the study, corresponding to 8 patients/site (the eligibility criteria are described in Table S1).

The study included four visits: (1) SV (screening visit); (2) V0 (baseline visit, before initiation of CVT-301); (3) V4w (4 weeks ± 7 days; telephonic visit); (4) V12w (12 weeks ± 14 days; end of the observational period). Two clearly differentiated methodological parts were contemplated. First (Part 1), an evaluation was conducted using different scales to measure the change in the primary variable and other secondary variables after 3 months of CVT-301 treatment. Second (Part 2), the change in the patient's motor and non-motor status was also evaluated at each hospital center at V12w before and after CVT-301 administration.

At SV (−5 to −10 days before V0), an informed consent was signed, and the Hauser's diary was given to the patient to complete at home. After inclusion in the study, all participants received detailed instructions on the PD home diary (Hauser's diary) [14]. At V0, Hauser's diary was collected with the information for the two consecutive days before the visit, and different clinical scales were administered: the 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) [15]; Modified Hoehn & Yahr stage [16] in OFF and ON state; Unified Parkinson's Disease Rating Scale (UPDRS) [17] part IV (UPDRS-IV); International Parkinson and Movement Disorder Society Nonmotor Rating Scale (MDS-NMS) Spanish version [18]; Schwab and England Activities of Daily Living Scale (ADLS) [19] during the OFF state (ADLS-OFF) and during the ON state (ADLS-ON); EUROHIS-QOL 8-item index (EUROHIS-QOL8) [20]; PQ-10 [21]; and Clinical Global Impression Scale Severity (CGI-S) [22] regarding the patient and the neurologist's opinion. As a mandatory indication, the patient should be trained at the clinic in this visit to use CVT-301 at the time an OFF episode appears. In this way, the neurologist observed the use of the device by the patient and the response and tolerability to the drug, correcting what was necessary in its use. From the next day to V0, the patient could use CVT-301 for OFF episodes. The patient was given a calendar to fill out, noting down each time he/she used CVT-301, the dose, the time, and the time it took to perceive the response. V4w was conducted by phone with the aim of monitoring the proper usability of CVT-301 and also to ask about safety (adverse drug reactions) and tolerability.

At V12w, the patient was assessed at the center during the OFF state and 30, 60, and 90 min after the administration of CVT-301. Two scales were administered at those exact 4 times: the UPDRS part III (UPDRS-III) [16] and a 10-item non-validated specifically designed scale to evaluate as exploratory observations the change from the OFF to the ON state in 10 NMS (NMSS-OFF/ON). This scale was administered by the neurologist by directly asking the patient about his/her symptoms at that precise moment. For each item, the options were: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms; and 4, very severe symptoms (i.e., from 0 to 4). The NMS included in the NMSS-OFF/ON were selected according to the literature [23]: (1) pain; (2) bad mood; (3) anxiety; (4) fatigue; (5) dizziness; (6) akathisia; (7) dysphagia; (8)

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mind dullness; (9) bladder urgency; and (10) sweating. A total score was calculated from the sum of the score for each item (from 0, minimum, to 40, maximum) (Table S2). Second, and while the patient was in the ON state as it was done at V0, the following scales were applied: PDQ-39; UPDRS-IV; MDS-NMS Spanish version; EUROHIS-QOL8; PQ-10; ADLS; and Clinical Global Impression Scale Improvement (CGI-I) [24] regarding the patient and the neurologist's criteria. In addition, Hauser's diary and the calendar on the use of CVT-301 completed by the patient were also collected.

CVT-301 could be administered by the patients according to daily clinical practice based on the product data sheet. Patients should be on a stable levodopa/dopa-decarboxylase inhibitor (e.g., carbidopa or benserazide) regimen before starting CVT-301. Patients selected for treatment with CVT-301 should be able to recognize the onset of their OFF symptoms and be capable of preparing the inhaler or else have a responsible caregiver able to prepare the inhaler for them when required. CVT-301 was to be inhaled when the patient noticed the reappearance of symptoms, motor or non-motor, of an OFF episode. The recommended dose of CVT-301 was 2 hard capsules up to 5 times per day, each delivering 33 mg of levodopa. The maximum daily dose of CVT-301 should not exceed 10 capsules (330 mg). During follow-up, no other medication other than CVT-301 should be modified (routine, dose, etc.) unless the neurologist considered these changes absolutely necessary. All the changes, including PD- and non-PD-related medications and levodopa equivalent daily dose (LEDD) [25], were recorded.

The safety data set consists of all subjects for whom the study device was initiated. Safety analyses were assessed by adverse events (AEs). All AEs were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment emergent AEs by MedDRA system organ class and preferred term, by severity, and by relationship to study treatment as assessed by the investigator were provided for all subjects. Finally, a free-flowing question was conducted about the best and worst aspects of CVT-301 with the intention of understanding the general opinion on positive and negative aspects of the product and its potential usability.

2.1 | Statistical Analysis

Data were processed using SPSS 20.0 for Windows. Different variables were expressed as quantitative and/or qualitative variables. Distribution for variables was verified by a one-sample Kolmogorov–Smirnov test. The primary efficacy outcome was the change from baseline (V0) to the end of the observational period (V12w) in the PDQ-39 total score. Secondary efficacy measures were the change from V0 to V12w in the daily OFF time (mean of 2 previous days to the visit according to Hauser's diary), UPDRS-IV, MDS-NMS total score, MDS-NMS NMF (non-motor fluctuations) total score, ADLS-OFF, ADLS-ON, EUROHIS-QOL8, and PQ-10, and the CGI-I at V12w.

Analyses on efficacy variables of Part 1 were performed with the Full Analysis (ITT) data set (all subjects who received at least 1 dose of CVT-301 and presented the data collected for the variable at V0 and V12w). First, a Wilcoxon signed-rank was performed for testing the change from baseline. To evaluate the magnitude of the change, in addition to the difference between V12w and V0, the relative change [$RC = (\text{mean } Test_{V12w} - \text{mean } Test_{V0}) \times 100/\text{mean } Test_{V0}$] [26] and Cohen's d_{av} effect size [$ES = (\text{mean } Test_{V12w} - \text{mean } Test_{V0})/(SD_{V12w} + SD_{V0}/2)$] [27] were calculated. The effect size was considered: ignored, <0.2; small, $0.2-<0.5$; moderate, $0.5-<0.8$; large, 0.8–1.3; very large, ≥ 1.3. A second analysis was conducted using a general linear model (GLM) repeated measures without and, thirdly, with adjustment to covariates (age, sex, disease duration, LEDD, and mean daily use of CVT-301). The same methodology (i.e., the 3 analyses) was applied to evaluate the change at V12w in the UPDRS-III and the NMSS-OFF/ON from OFF to 30, 60, and 90 min after CVT-301 administration (Part 2). Values of $p < 0.05$ were considered statistically significant. A p-value less than 0.05 in the 3 analyses proposed simultaneously was considered indicative of a significant change from the baseline visit to the final visit for each proposed variable.

2.2 | Standard Protocol Approvals, Registrations, and Patient Consents

For this study, we received approval from the *Comité de Ética de Investigación de medicamentos de Galicia (CEImG)* from Spain (November 29, 2023). Written informed consent from all patients in this study was obtained.

3 | Results

A total of 44 patients were selected to participate between March 2024 (first patient, March 5) and July 2025 (last patient, July 14). Four patients were excluded from participation, resulting in a final sample of 40 patients (age 62.3 ± 9.2 years; 55% males) who completed the baseline visit (V0) (Figure S1). The mean time from PD diagnosis at V0 was 8.5 ± 5.3 years. All patients had motor fluctuations, whereas 85% and 45% had NMF and dyskinesia, respectively. A majority of the patients were receiving levodopa in combination with another dopaminergic drug, and none had received an on-demand therapy or a device-aided therapy before (Table 1). At baseline, 75% and 64.1% of the patients were classified as from "moderately ill" to "severely ill," according to the opinion of the neurologist and their self, respectively (Figure S2A).

At 12 weeks, 34 out of 40 patients (85%) were using CVT-301 and completed the follow-up. Of the 6 patients who dropped out, 4 did so due to drug-related side effects, 1 due to difficulties using the device, and 1 due to switching to a device-aided therapy (subcutaneous apomorphine) (Figure S1). Changes in the previous treatment were done only in 2 patients who completed the study (one withdrew opicapone and the other added 1 pill of levodopa retard at night). The mean daily use of CVT-301 was 1.3 ± 0.9, being 1.3 ± 1.0 the week before the final visit (V12w) ($N = 31$). Only 3 patients used it up to a maximum of 4 times in 1 day, and 1 patient up to 5 times. The average number of days that CVT-301 was not administered was 25.9 ± 28.2. With respect to the administration schedule, the percentage of administrations was 43%, 51.4%, and 5.6% between 08:00 and 14:00 h, 14:01 and 23:59 h, and 00:00 and 07:59 h, respectively.

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TABLE 1 | Data about sociodemographic aspects, comorbidities, PD, antiparkinsonian drugs and other therapies at baseline (V0) ($N = 40$).

Age	62.3 ± 9.2 (43–77)
Gender (males) (%)	55
Weight (kg)[a]	79.7 ± 18.9 (53–129)
Height (cms)[a]	167.7 ± 9.7 (146–189)
BMI[a]	28.2 ± 5.3 (19–39.5)
Caucasian race (%)	97.5
Civil status (%)	
Married	85
Single	7.5
Widowed	5
Divorced	2.5
Level of education (%)	
Primary	25
Secondary	45
University	30
Living style (%)	
With the partner	80
Alone	12.5
With another family member	5
Other	2.5
Comorbidities (%)	
Arterial hypertension	30
Diabetes mellitus	5
Dyslipemia	27.5
Atrial fibrillation/arrythmia	15
Ischemic cardiomyopathy	5
Hypertensive cardiomyopathy	5
Pulmonary disease	0
Active smoking	10
Time from diagnosis (years)	8.5 ± 5.3 (1.7–25)
Age at symptoms onset	54.2 ± 8.3 (40–71)
Daily OFF time (h)	4.3 ± 2.2 (2.25–11.25)
H&Y—OFF	2 [2, 2]
H&Y—ON	2 [1, 2]
Motor fluctuations (%)	100
Non-motor fluctuations (%)	85
Dyskinesia (%)	45
Mild cognitive impairment (%)	5
Psychosis (%)	2.5
Treatment for PD (%)	
Immediate-release L-dopa	100
Extended-release L-dopa	40
Dopamine agonist	60
MAO-B inhibitor	90
COMT inhibitor	50
Amantadine	10
OdT previously (%)	0
DAT previously (%)	0
L-dopa daily dose (mg)	631.9 ± 245.2 (300–1200)
LEDD (mg)	1031.9 ± 395.7 (450–2075)
Other treatments (%)	
Antidepressant	30
Benzodiazepine	27.5
Antipsychotic	2.5
Anti-dementia	2.5
Active exercise (%)	52.5

Note: The results represent %, mean ± SD (range) or median [p25, p75].
Abbreviations: BMI, body mass index; COMT, catechol-O-methyl transferase; DAT, device-aided therapy; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dose; MAO, monoamine oxidase.
[a]$N = 34$ (for the rest of variables, $N = 40$).

Regarding the primary endpoint, the PDQ39 total score decreased by 27.9%, from 43.6 ± 24.2 at V0 to 31.4 ± 20.6 at V12w ($N = 34$; $p < 0.0001$). A significant decrease was observed in the mean score of 4 domains of the PDQ39: "Mobility" (RC −31.5%); "Activities of daily living" (RC −31.0%); "Communication" (RC −37.2%); and "Bodily discomfort" (RC −24.1%) (Table S3 and Figure 1). On the contrary, no significant changes were detected from V0 to V12w in GQoL (EUROHIS-8 and PQ-10) (Table 2). Mean daily OFF time decreased from V0 to V12w by 1.6 ± 1.9 h ($N = 33$; $p < 0.0001$) (Table 2). However, the change from V0 to V12w in the rest of the secondary variables did not show statistical significance (Table 2). Specifically, no significant change was detected in any of the MDS-NMS domains except for M ("Other"), which includes physical and mental fatigue (Table S3 and Figure 2). No significant changes were also detected between the two visits, V0 and V12w, in the change experienced by patients for each of the items of the MDS-NMS NMF subscale (from 0, no change, to 4, large change) (Figure 2).

At V12w, NMS burden (NMSS-OFF/ON total score) was reduced from the OFF state to 30, 60, and 90 min after using CVT-301 ($N = 34$; $p < 0.0001$) (Figure 3). By items, a significant decrease in the score was detected in all moments of the evaluation (30, 60, and 90 min after the administration of CVT-301) in bad mood, fatigue, dizziness, mind dullness, and sweating; after 60 and 90 min in pain; and after 30 min in akathisia (Table S4 and Figure 4). No changes were detected after using CVT-301 in dysphagia and

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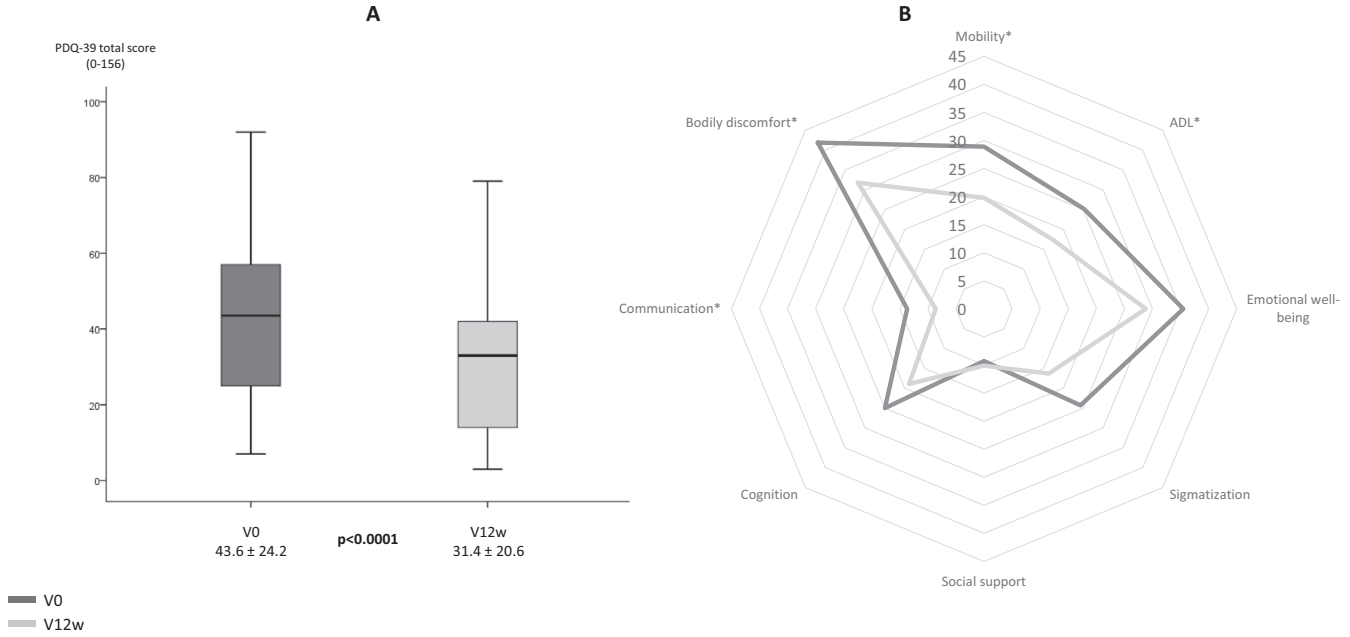

FIGURE 1 | (A) Change in the PDQ-39 total score from baseline (V0) to week 12 ± 2 weeks (V12w) in PwP treated with CVT-301 ($N = 34$). Data are presented as box plots, with the box representing the median and the two middle quartiles (25%–75%). (B) Mean value of each domain of the PDQ-39 at V0 (dark gray) and at V12w (light gray) ($N = 34$). *$p < 0.005$; the result was significant in "Mobility," "ADL," "Communication," and "Bodily discomfort" ($p < 0.05$ for the three analyses proposed in methods). ADL, activities of daily living.

TABLE 2 | Analysis of the primary and secondary efficacy outcomes (change from V0, before starting to use CVT-301, to V12w, 12 ± 2 weeks after starting to use CVT-301).

Clinical characteristics	*N*	V0	V12w	RC (%)	*d*	p_a	p_b	p_c
Primary endpoint								
PDQ-39	34	43.6 ± 24.2	31.4 ± 20.6	−27.9	0.83	**< 0.0001**	**< 0.0001**	**< 0.0001**
Secondary endpoints								
Mean daily OFF time (Hauser diary)	33	4.4 ± 2.3	2.7 ± 1.7	−38.6	0.83	**< 0.0001**	**< 0.0001**	**< 0.0001**
UPDRS-IV	34	4.7 ± 1.9	4.0 ± 1.8	−17.5	0.28	0.135	0.107	**0.043**
MDS-NMS total score	34	132.4 ± 88.8	111.7 ± 84.7	−15.6	0.26	**0.033**	0.134	0.058
MDS-NMS NMF total score	30	13.2 ± 15.8	10.2 ± 12.2	−22.7	0.21	0.212	0.248	0.288
ADLS-OFF	28	78.4 ± 12.6	83.6 ± 6.8	6.6	0.37	**0.044**	0.063	0.092
ADLS-ON	33	90.9 ± 9.7	92.4 ± 8.6	1.7	0.28	0.101	0.115	0.164
EUROHIS-QOL 8-item index	34	28.5 ± 4.7	29.0 ± 5.0	1.8	0.11	0.417	0.507	0.153
PQ-10	34	6.8 ± 1.7	7.0 ± 1.7	2.9	0.09	0.629	0.599	0.363

Note: The results represent mean ± SD; RC, relative change; *d*, Cohen's *d* effect size; p_a, comparison between V12w (12 ± 2 weeks after starting to use CVT-301) and V0 (baseline, before starting to use CVT-301) after using the Wilcoxon signed-rank test; p_b, comparison between V12w and V0 after using general linear models (GLM) repeated measures; p_c, comparison between V12w and V0 after using GLM repeated measures with adjustment to covariates (age, sex, disease duration, LEDD, and mean daily use of CVT-301). In bold, $p < 0.005$.
Abbreviations: ADLS, the Schwab and England Activities of Daily Living; MDS-NMS, International Parkinson and Movement Disorder Society Nonmotor Rating Scale; NMF, non-motor fluctuations; PDQ-39, 39-item Parkinson's disease Quality of Life Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale.

bladder urgency (Table S4 and Figure 4). In addition, a significant reduction in the UPDRS-III score was also detected at 30, 60, and 90 min after receiving CVT-301 compared to before receiving it (OFF state) ($N = 34$), with the maximum mean reduction value being 14.1 ± 7.8 points 30 min after post-dose (Figure 3). Moreover, 80% of the patients improved according to the CGI-I at V12w (Figure S2B).

A total of 18 adverse events were reported in 15 patients (37.5%), all but one (dyskinesia) of which were classified as related to CVT-301 (Table 3). The most frequent adverse event was cough, reported in 11 patients (27.5%). No severe adverse events were reported, and 66.7% (4 out of 6) of the dropouts were due to an adverse event, with cough in 3 cases and headache with itchy throat in the other. In a free survey about the best and worst of

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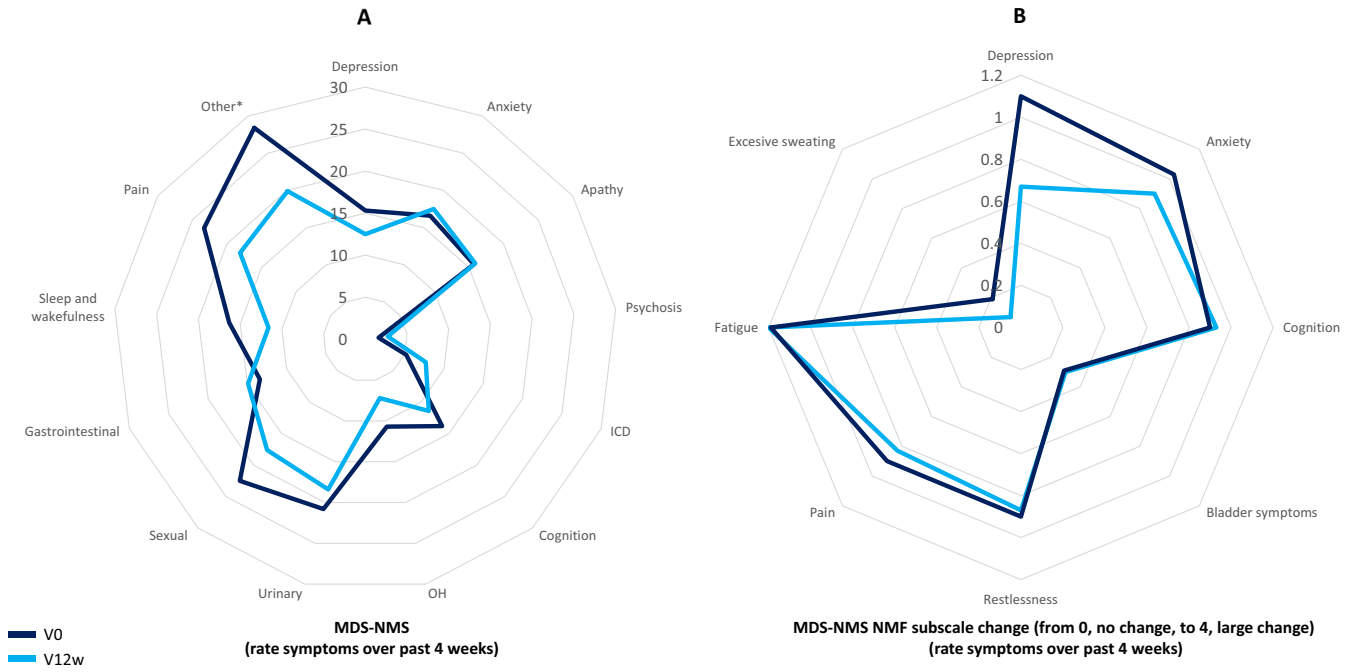

FIGURE 2 | (A) Mean value of each domain of the MDS-NMS at V0 (dark blue) and at V12w (light blue) ($N = 34$). *$p < 0.005$; the result was significant in "Other" ($p < 0.05$ for the three analyses proposed in methods). (B) Mean value of each domain of the MDS-NMS NMF subscale at V0 (dark blue) and at V12w (light blue) ($N = 34$). No significant differences were detected for any item.

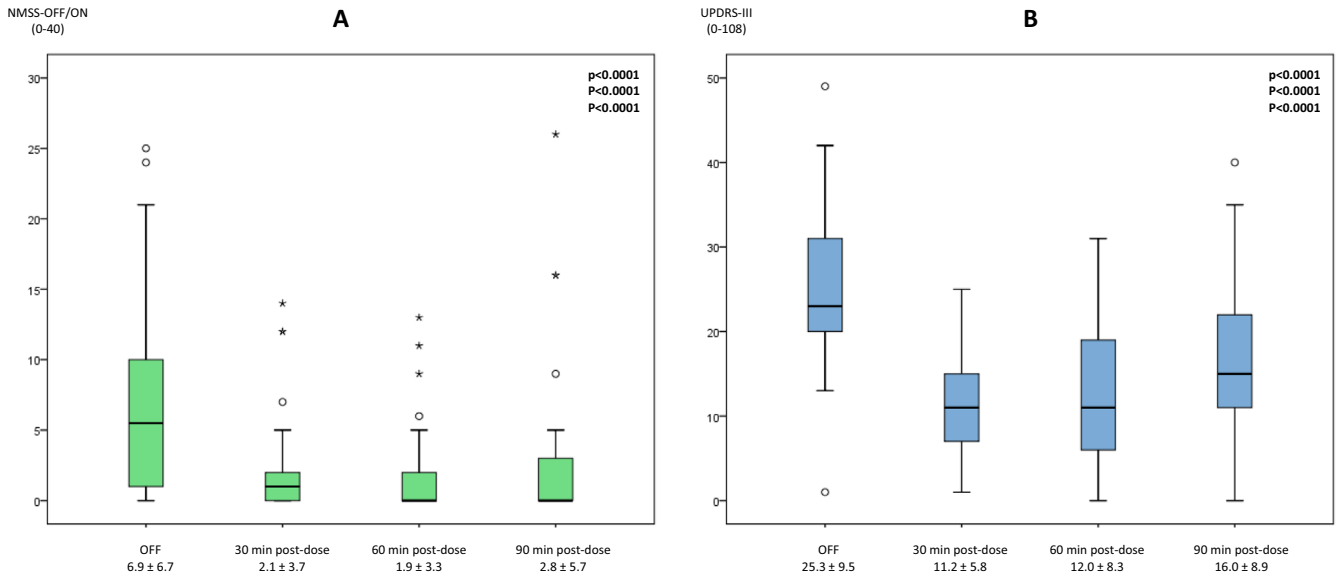

FIGURE 3 | Change at week 12 ± 2 weeks in the NMSS-OFF/ON total score (A) and in the UPDRS-III (B) from the OFF state (pre- CVT-301) to 30, 60, and 90 min after administration of CVT-301 ($N = 34$); $p < 0.0001$ for all comparisons after applying the three analyses proposed in methods: 30 min after CVT-301 vs. OFF; 60 min after CVT-301 vs. OFF; and 90 min after CVT-301 vs. OFF. Data are presented as box plots, with the box representing the median and the two middle quartiles (25%–75%). Mild outliers (o) of (Q1 − 1.5 × IQR) (lower) or (Q3 + 1.5 × IQR) (upper), but not as far as (Q1 − 3 × IQR) or (Q3 + 3 × IQR), which define extreme outliers (*). NMS, non-motor symptoms; NMSS-OFF/ON, Non-Motor Symptoms Scale—OFF/ON; UPDRS, Unified Parkinson's Disease Rating Scale.

CVT-301, the most frequent answers were the speed of the effect as the best and the annoying sensation of the powder in the throat as the worst. On a scale of 0 (worst) to 10 (best), the ease of use of the device was rated with an average score of 7.6 ± 1.4 ($N = 34$), ranging from 4 to 10 (70% scored ≥ 7).

4 | Discussion

The present study observed that the use of CVT-301 by PwP was associated with an improvement in their HRQoL after 3 months of follow-up. Despite the methodological limitations of its design

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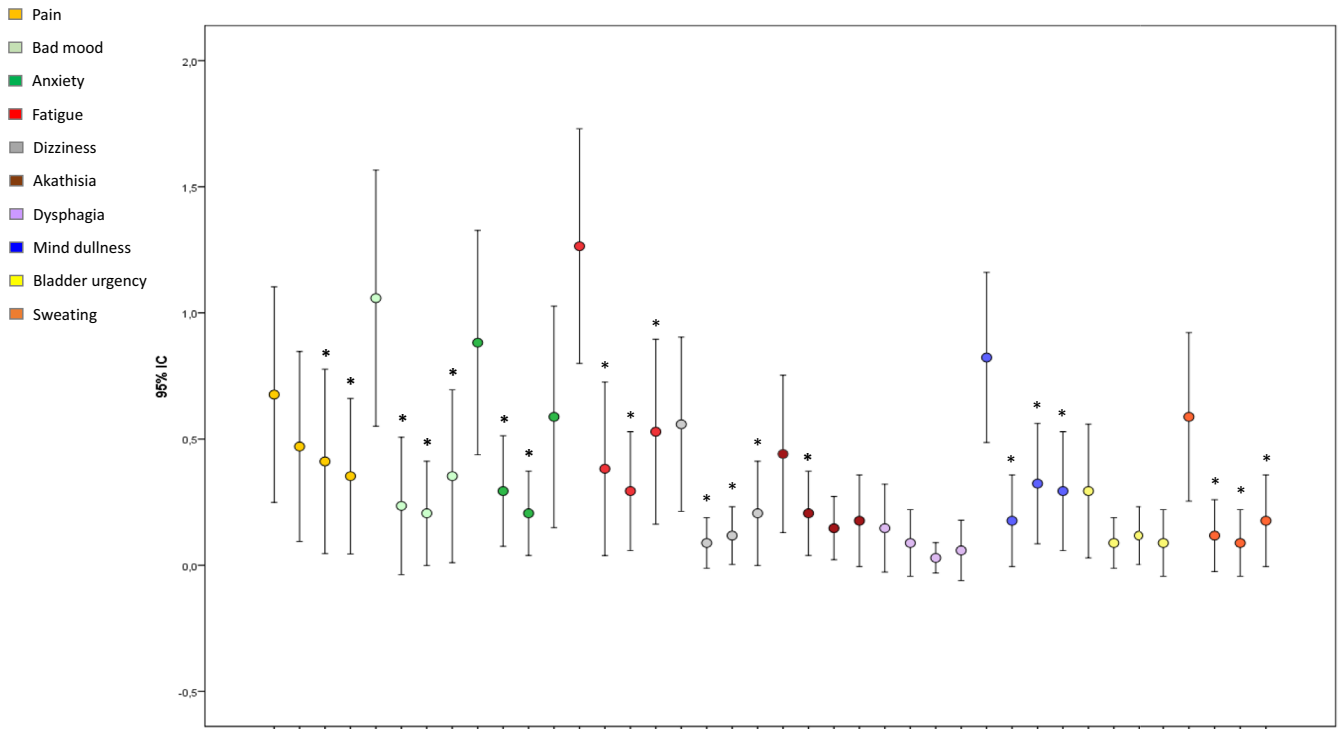

FIGURE 4 | Mean value and standard deviation for each item (score from 0 to 4) of the NMSS-OFF/ON in the OFF state and 30, 60, and 90 min (from the left to the right for each item) after the administration of CVT-301. *$p < 0.05$ for the three analyses proposed in methods.

TABLE 3 | Adverse events collected by the neurologist in patients receiving CVT-301 from V0 to V12w ($N = 40$).

	N
Total AEs, N	18
Cough	11
Itchy throat	2
Phlegm	1
Nausea	1
Dry mouth	1
Headache	1
Dyskinesia	1
SAEs, *N*	0
Patients with at least one AE, *N* (%)	15 (37.5)
At least possibly related (CVT-301) AEs, *N*	17
Patients with at least possibly related (CVT-301) AEs, *N* (%)	14 (35)
Patients with at least one AE leading to discontinuation, N (%)	4 (10)
Cough	3
Headache and itchy throat (the same patient)	1
Patients with at least one possibly related (CVT-301) leading to discontinuation, *N* (%)	4 (10)
Deaths, *N* (%)	0 (0)

Note: The results represent *N* or *N* (%).
Abbreviations: AEs, adverse events; SAEs, severe adverse events.

(open study), the study collected data on daily clinical practice, and this finding is relevant and novel given that it had not been previously explored. In addition, two other novel observations were found. First, the effect on motor signs (UPDRS-III) lasted up to 90 min. Second, there was also an improvement in NMS associated with the OFF state.

CVT-301 has demonstrated efficacy in clinical trials for the rapid treatment of OFF episodes in PwP who are already receiving oral levodopa/carbidopa. In a phase 3 randomized, double-blind, placebo-controlled trial, CVT-301 at an 84 mg dose produced a statistically significant improvement in motor function, as measured by the change in UPDRS-III Part III at 30 min post-dose compared to placebo (least-squares mean difference −3.92; $p = 0.0088$) [7]. The onset of benefit was observed as early as 10 min post-inhalation, and the effect was maintained for at least 60 min, with a mean maximum decrease in the UPDRS-III in the group receiving CVT-301 slightly above 10 points. In a randomized 12-month pulmonary safety study, the mean reduction in the UPDRS-III score was about 15 points at 30 and at 60 min post-dose even after 52 weeks using the drug [10]. But the effect at 90 min post-dose had not been previously explored. Here, we observed a mean maximum reduction of 14.1 points at 30 min post-dose with a still significant reduction of 9.3 points even after 90 min of its administration.

In addition, the motor improvement was accompanied by an improvement in the burden of NMS present during the OFF state as well. Previous studies with CVT-301 did not include dedicated assessments of NMS as primary or secondary endpoints, nor did they report significant changes in non-motor domains such as mood, sleep, autonomic function, or cognition. Using a non-validated proposed scale (NMSS-OFF/ON),

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we found significant improvement in NMS from OFF to 30, 60, and 90 min post-dose, with specific benefit in pain, bad mood, anxiety, fatigue, dizziness, akathisia, mind dullness, and sweating but not in dysphagia or bladder urgency. The present study also suggests the importance of evaluating in PwP with clinical fluctuations the change from the OFF to the ON state not only of motor symptoms but also of NMS. In other words, to assess motor and non-motor fluctuations but with real-time quantification of both (symptoms and/or signs) [28–30]. To our knowledge, this aspect was only recently explored in a study of 310 French PD patients treated with deep brain stimulation [31]. Faggianelli et al. [31] included 11 NMS in a questionnaire allowing a real-time quantification of the severity, ranging from 0 to 10, of NMS and their fluctuation with levodopa, detecting that each NMS was significantly improved by L-Dopa. Unlike them, we decided not to use a 0–10 scale, which we believe is more difficult to assess, but rather to categorize by severity (none vs. mild vs. moderate vs. severe vs. very severe). Furthermore, we measured the changes 30, 60, and 90 min after CVT-301 administration, with a behavior in response observed similar to motor changes. Like Faggianelli et al. [31], we detected a very high percentage of patients with NMS and similar results in the change of some very pronounced symptoms, such as fatigue or mood. Although it should be corroborated in studies specifically designed for this purpose, our findings suggest the possibility that CVT-301 could be useful in improving NMF in PD patients. On the other hand, we believe that information gathered in this way is more useful than when asking about the patient's perception of change in NMS during the previous weeks (i.e., MDS-NMS NMF). In our cohort, although the score on the MDS-NMS and MDS-NMS NMF was lower after 3 months of using CVT-301, the change was not significant. Of course, this methodology for assessing changes in NMS perception should be validated in future controlled studies designed for this purpose.

The present study was positive for the primary endpoint, demonstrating a benefit in HRQoL for PwP treated with CVT-301. We had hypothesized that PD HRQoL could improve in PwP with the use of CVT-301 due to a reduction in OFF time and severity of OFF episodes (motor symptoms and NMS). Despite the fact that the mean use of CVT-301 in our study was low (1.3 times/daily), mean daily OFF time decreased by 1.6 ± 1.9 h. OFF time was not reduced in previous clinical trials except in a phase 2 RCT conducted in 86 patients (43 CVT-301 vs. 43 placebo) that used the study drug at an average frequency of 2.1 times per day, finding at 4 weeks least-squares mean OFF-time change from baseline favored CVT-301 by 0.9 h per day (1.6 vs. 0.8; $p = 0.045$) [6]. Importantly, the dose administered of CVT-301 at that visit in this trial was equivalent to 84 mg, the dose commercialized for use in daily clinical practice. If one administration of CVT-301 (84 mg, 2 capsules) produces a benefit of at least 90 min, it is expected that proper use could at least reduce OFF time by 1.5 h with one administration per day, as we observed, and the improvement during that time in motor and NMS could improve, secondarily, the HRQoL. Improvement in areas such as mobility, ADL, communication, and bodily discomfort would reflect the motor and non-motor improvement that PwP achieve for at least 90 min with its administration. Moreover, and in agreement with other studies, a high percentage of patients improved according to the GCI [5, 7, 32].

In addition to the above, in this study CVT-301 demonstrated a good safety and tolerability profile as already reported [4–10, 32]. However, it should be noted that coughing is a common symptom, affecting more than one in four patients in our study, and that up to 12.5% discontinued treatment due to inhalation-related side effects and/or limitations in device use. These data reinforce the importance of thorough training on device use in clinical practice [33].

This study has some limitations. First, there are limitations inherent to the methodology itself (open study without randomization and placebo group), and the study was also not blinded to the patient status (ON/OFF). Second, the tool we used to assess the change in NMS from the OFF to the ON state has not been validated. Third, the study was conducted in a small cohort of PwP ($N = 40$) and not in a large cohort with many patients. Fourth, the follow-up period is not very long, and it would be interesting to know the change in QoL after longer use over time (e.g., > 1 year). Fifth, although the present study was developed from a clear hypothesis that links the possible reduction of OFF time and the severity of OFF episodes with an improvement in QoL, the proposed design does not strictly allow this to be demonstrated, and the findings should be interpreted with caution. Sixth, an underestimation in the reporting of adverse events cannot be ruled out. Finally, other important limitations are the lack of control for expectancy effects, possible center-level variability in open-label assessment, multiplicity of testing, and the possibility that tolerability-related discontinuation may bias the observed benefit among completers. However, despite these limitations, the present study introduces new knowledge about the effect of CVT-301 on PwP not previously reported.

In summary, in this prospective open-label multicenter study, use of inhaled levodopa was associated with improvement in HRQoL and selected OFF-related NMS in PwP over 12 weeks. Acute motor and non-motor benefits were also observed up to 90 min after administration, but these findings require confirmation in controlled studies.

Author Contributions

Diego Santos García: conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, visualization, writing – review and editing, formal analysis, data curation, supervision, resources. **Maria Icíar Cimas Hernando:** investigation, writing – review and editing. **Rosa Yáñez Baña:** investigation, writing – review and editing. **María Cerdán Sánchez:** investigation, writing – review and editing. **Iria Cabo:** investigation, writing – review and editing.

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Conflicts of Interest

Diego Santos-García has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, Teva, Archímedes, Esteve, Stada, Orion Pharma, financial compensation for INIBIC/Fundación Professor Novoa Santos in relation to activity as PI in phase 2 to phase 4 clinical trials for Parkinson's disease and other movement disorders, compensation for Fundación Degen in relation to different projects, and grants from the "Fundación Professor Novoa Santos" as a result of the "CONVOCATORIA DE AYUDAS PARA LA REALIZACIÓN DE PROYECTOS DE INVESTIGACIÓN PARA GRUPOS EMERGENTES Y ASOCIADOS DEL INIBIC (2023/2024)." María Cerdán Sánchez has received honoraria for educational presentations by Abbvie, KRKA, Zambon, Bial, Italfarmaco, Esteve and Stada. Rosa Yáñez Baña has received honoraria for educational presentations and advice service by Abbvie, Esteve, italfarmaco, Bial, Stada, and Orion Pharma. Iria Cabo has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, Italfarmaco, Teva, Esteve, Stada, and Orion Pharma. Maria Icíar Cimas-Hernando has nothing to report.

Data Availability Statement

The protocol and the statistical analysis plan are available on request. Deidentified participant data are not available for legal and ethical reasons.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flowchart showing patients selected to participate in the study, screening failures, and dropouts throughout the follow-up. **Figure S2:** CGI-S at V0 and CGI-I at V12w according to the opinion of the neurologist and the patient. **Table S1:** Inclusion and exclusion criteria of the INLEVO-LIFE PD study (an open-label study of the effect of INhaled LEVOdopa on quality of LIFE in Parkinson's Disease). **Table S2:** The NMSS-OFF/ON was specifically designed to assess the NMS burden during the OFF and during the ON state. This scale should be administered by the neurologist by directly asking the patient about his/her symptoms at that precise moment. For each item, only one option is possible (from 0 to 4). The NMSS-OFF/ON total score is the result of the sum of each item, from 0 (10 × 0) to 40 (10 × 4). **Table S3:** Analysis of the domains and/or items of the PDQ-39, MDS-NMS and EUROHIS-QOL 8-item index (change from V0, before starting to use CVT-301, to V12w, 12 ± 2 weeks after starting to use CVT-301). **Table S4:** Relative change in the score of each item of the NMSS-OFF/ON after 30, 60, and 90 min of the administration of CVT-301 in the hospital at V12w.

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