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Short communication

Motor and nonmotor symptoms in patients treated with 24-hour daily levodopa-carbidopa intestinal gel infusion: Analysis of the COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel (COSMOS)

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ABSTRACT

Introduction: Patients with advanced Parkinson's disease (APD) commonly experience motor and nonmotor symptoms (NMS) associated with functional limitations and decreased quality of life. We compared motor and nonmotor outcomes in patients with APD receiving 24- versus 16-h levodopa-carbidopa intestinal gel (LCIG).
Methods: Data from COSMOS, a large, real-world, retrospective and cross-sectional, observational study on LCIG and comedication in APD were obtained from medical records and a single patient visit for patients receiving 24- and 16-h LCIG infusion. Changes from baseline were evaluated for motor symptoms, NMS, and clinical characteristics. Safety was also assessed.
Results: Data for 401 patients were included in this subanalysis. At the patient visit there were 35 patients on 24-h LCIG and 366 on 16-h LCIG. "Off" time and dyskinesia (duration and severity) were reduced in both groups. In both LCIG treatment groups, prevalence of most symptoms was reduced. There were significant differences in the change from baseline in severity and frequency of freezing of gait with 24-h LCIG versus 16-h LCIG ($p = 0.011$ and $p = 0.038$), severity of urinary symptoms ($p = 0.006$), and frequency of cognitive impairment ($p = 0.014$) with 24-h LCIG versus 16-h LCIG. Adverse events were similar for both treatment groups and considered tolerable.
Conclusions: LCIG 24-h infusion may be a useful treatment option, when clinically justified, for select patients with APD.
Clinical trial number: NCT03362879.

1. Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disease [1]. Oral levodopa/dopa decarboxylase inhibitor combinations are standard treatment for PD [2,3]. After 4–6 years of oral levodopa, approximately 40%–75% of patients develop motor symptom fluctuations, dyskinesias, and a variety of nonmotor symptoms (NMS) [2,4]. Oral levodopa has a short half-life and is poorly absorbed

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due to erratic gastric emptying, a problem that can become more paramount with age, leading to fluctuating levodopa levels in plasma [4–6]. Fluctuating levodopa concentrations cause pulsatile striatal dopamine receptor activation, which differs from typical continuous dopamine receptor activation under normal physiological circumstances [7,8].

Levodopa-carbidopa intestinal gel (LCIG) is delivered continuously to the upper intestine most commonly over 16 waking hours, ensuring more stable levodopa plasma concentrations than standard oral levodopa therapy [4]. As LCIG improves dyskinesias and motor symptoms in patients with PD [8,9], 24-h LCIG may be an alternative treatment solution particularly for nighttime or early-morning symptom fluctuation [9]. Further, 24-h LCIG provides a simplified dose regimen, potentially improving nonadherence, which is common in some patients with PD [10]. Despite availability of LCIG in Europe for 17 years and numerous trials demonstrating efficacy and safety [9,11–15], there is little real-world evidence on 24-h LCIG. Additional safety and efficacy studies are required for 24-h LCIG infusion versus standard 16-h LCIG infusion.

COmedication **S**tudy assessing **M**ono- and c**O**mbination therapy with levodopa-carbidopa inte**S**tinal gel (COSMOS) was a large, multinational study evaluating real-world use of LCIG in routine clinical practice [16]. This subanalysis of COSMOS described clinical outcomes with 24-h versus 16-h LCIG in patients with advanced PD (APD).

2. Methods

2.1. Study design

COSMOS was a multinational, retrospective and cross-sectional, post-marketing, observational study in patients with APD treated with LCIG in routine practice setting (full methodology published [16]). Patients with APD treated with LCIG for ≥12 months were included. Data were collected by retrospective review of patient data from medical records and at a single patient visit. For this analysis, patients were stratified by LCIG daily duration at patient visit (24 h vs ~16 h [referred to as "16 h"]). Each patient or legal authorized representative provided written informed consent prior to any data collection. All procedures were completed in accord with ethical standards of Independent Ethics Committees or Institutional Review Boards of the institution where data were collected.

2.2. Demographics and clinical characteristics

Data were collected at the patient visit on patient demographics, medical PD history, and LCIG infusion variables. PD medications were assessed before LCIG initiation and during the LCIG infusion period, and documented in clinical records.

2.3. Clinical assessments and LCIG dosing

Patients underwent structured interviews to obtain information for clinical assessments, which were part of routine clinical practice and part of standardized, prospective protocol. The physician-assessed Unified Parkinson's Disease Rating Scale (UPDRS) was used to measure "off" time (Part IV item 39, modified), dyskinesia duration (Part IV item 32, modified), and dyskinesia severity (Part IV item 33) both before LCIG initiation and at patient visit (cross-sectionally). At patient visit, physicians collected cross-sectional information for presence, severity rating (none, mild, moderate, or severe), and frequency rating (rarely, often, frequent, or very frequent) of motor symptoms, nonmotor symptoms (NMS), and treatment-related symptoms from both timepoints, via clinical records before LCIG initiation and at patient visit. Symptoms were defined as characterized with the PD composite scale [17]. LCIG dosing and infusion-related dosing parameters were evaluated as part of routine clinical practice for patients who received 24-h LCIG at any timepoint.

2.4. Safety

Data from safety assessments previously collected from healthcare professionals for other purposes were used to document adverse events (AEs) that had a reasonable possibility of being causally related to the treatment drug or device. AEs of special interest were noted at LCIG initiation and during LCIG maintenance treatment.

2.5. Statistical analysis

Data from medical records and patient visits were analyzed using descriptive statistics. All statistical analyses were achieved using SAS® version 9.4 (SAS Institute, Inc., Cary, NC, USA). For motor symptoms, NMS, and treatment-related symptoms, ratings of frequency and severity were transformed into numerical scores and analyzed. For each symptom, variables 'severity' and 'frequency' were transformed as follows: for the transformed severity variable 'no symptom' was 0, mild = 1, moderate = 2, and severe = 3, and unknown was set to missing. For the transformed frequency variable 'no symptom' was 0, rarely = 1, often = 2, frequent = 3, very frequent = 4, and unknown was set to missing. Additionally, prevalence, defined as percentage of patients affected, was analyzed for motor symptoms, NMS, and treatment-related symptoms. A chi-squared test compared categorical data when possible (eg, PD motor phenotype, monotherapy, and prevalence). The Kappa test analyzed motor symptom and NMS prevalence (within-group differences).

Logistic regression and subgroup analyses were applied to investigate factors related to 24-h LCIG. Potential prognostic factors used for regression modeling included demographic variables (eg, age, gender, race) and baseline disease characteristics at LCIG initiation (eg, PD history, motor symptoms, NMS, previous PD medication, and levodopa equivalent daily dose).

3. Results

3.1. Patients

3.1.1. Demographics and baseline clinical characteristics

A total of 412 patients were enrolled (3 were excluded because they did not meet the selection criteria and 8 were excluded from analysis because daily LCIG duration was not available). Of 401 patients, 35 (9%) received 24-h LCIG and 366 (91%) received 16-h LCIG at patient visit. Patients had PD durations of 14.8 and 15.8 years in the 24-h LCIG and 16-h LCIG groups. Use of 24-h LCIG was based on clinical judgement; most common reasons being nocturnal/morning akinesia (n [%], 22 [53.7%]), sleep problems (15 [36.6%]), and biphasic dyskinesia (5 [12.2%]). A numerically greater proportion of 24-h versus 16-h LCIG patients initiated LCIG for uncontrolled dyskinesia (60.0% vs 51.1%, Table 1). At baseline, though, characteristics were similar between groups; some symptoms were greater in patients receiving 24-h versus 16-h LCIG (eg, dystonia [prevalence and frequency], pain [prevalence, severity and frequency], and dysphagia [severity and frequency]) (Supplemental Tables 1 and 2).

3.2. Clinical assessments

3.2.1. Motor symptoms

The changes from baseline in "off" time and dyskinesia duration were reduced with both 24- and 16-h LCIG ("off" time change from baseline, mean ± SD, −5.4 ± 5.1 and −3.9 ± 4.2 h [$p < 0.0001$ for both] [baseline, mean ± SD, 7.4 ± 5.6 vs 5.9 ± 3.3]; dyskinesia duration, mean ± SD, −1.6 ± 3.1 h [$p = 0.0150$] and −1.9 ± 3.6 h [$p < 0.0001$]) (Supplemental Fig. 1). The corresponding additional "on" time without dyskinesia were +7.0 h and +5.8 h for 24-h and 16-h LCIG. There were reductions from baseline in dyskinesia severity with both 24-h and 16-h LCIG (mean ± SD, 24-h LCIG, −1.3 ± 1.4; 16-h LCIG, −0.8 ± 1.3, both $p < 0.001$) (Supplemental Fig. 1). There were no differences between

Table 1
Demographics and baseline clinical characteristics in patients with 24-h or 16-h LCIG at baseline or LCIG initiation.

Characteristic	24-h LCIG N = 35	16-h LCIG N = 366
Male, n (%)	21 (60.0)	241 (65.8)
Age at baseline, mean ± SD, years	66.5 ± 9.8	69.4 ± 7.6
Race, n (%)[a]		
White	35 (100)	362 (98.9)
Asian	0	2 (0.5)
Other	0	2 (0.5)
Disease history		
PD motor phenotype n (%)		
Akinetic rigid	12 (35.3)[b]	143 (39.1)
Mixed	11 (32.4)[b]	118 (32.2)
Tremor-dominant	11 (32.4)[b]	97 (26.5)
Unknown	0[b]	5 (1.4)
Other	0[b]	3 (0.8)
Morning akinesia present, n (%)	24 (75.0)[c]	248 (68.9)[d]
Wearing off present, n (%)	30 (90.9)[e]	341 (93.7)[f]
Dyskinesia present, n (%)	28 (84.8)[e]	304 (83.3)[g]
Time since PD diagnosis, mean ± SD, years	14.8 ± 4.5	15.8 ± 6.0
Reason for LCIG initiation, n (%)		
Disabling motor fluctuations/off periods	33 (94.3)	334 (91.3)
Decreased quality of life	20 (57.1)	210 (57.4)
Uncontrolled dyskinesia	21 (60.0)	187 (51.1)
Lack of efficacy of previous treatment	14 (40.0)	192 (52.5)
Safety	2 (5.7)	45 (12.3)
Other[h]	1 (2.9)	9 (2.5)
UPDRS total score, mean ± SD (n)	70.8 ± 30.2 (6)	56.9 ± 24.2 (111)
UPDRS Part IV item 39: "Off" time, mean ± SD, hours (n)	7.4 ± 5.6 (26)	5.9 ± 3.3 (247)
UPDRS Part IV item 32: Dyskinesia duration, mean ± SD, hours (n)	3.5 ± 3.8 (26)	3.8 ± 3.3 (238)
UPDRS Part IV item 33: Dyskinesia severity[i], mean ± SD (n)	1.9 ± 1.3 (32)	1.6 ± 1.2 (331)

[a] There were no patients who were Black or mixed race.
[b] N = 34.
[c] N = 32.
[d] N = 360.
[e] N = 33.
[f] N = 364.
[g] N = 365.
[h] Other reasons included the following: in the 24-h LCIG group, difficulty in medication balance (n = 1); in the 16-h LCIG group: facial dystonia (n = 1), gait impairment (n = 1), tremor (n = 1), severe "off" dystonia (n = 1), dolor (n = 1), severe dysphagia (n = 1), orthostatic hypotension due to oral levodopa (n = 1), sleeping disorders (n = 1), and patient desire to cease oral medications (n = 1).
[i] Dyskinesia severity was measured with the following scale: not disabling = 0, mildly disabling = 1, moderately disabling = 2, severely disabling = 3, completely disabled = 4, unknown.

LCIG, levodopa-carbidopa intestinal gel; N/A, not available; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

groups in changes from baseline in "off" time, dyskinesia duration, or dyskinesia severity.

Changes from baseline in prevalence, severity, and frequency for motor symptoms occurred with both 24-h and 16-h LCIG (Fig. 1A, Supplemental Figs. 2A and B, and Supplemental Table 1). There were reductions from baseline in prevalence of most motor symptoms with both 24-h and 16-h LCIG, with the exceptions of balance and dysphagia for 24-h LCIG and hypophonia and dysphagia for 16-h LCIG (Fig. 1A). Although prevalence of gait impairment decreased in both, a numerically greater reduction in prevalence of gait impairment occurred with 24-h versus 16-h LCIG (percentages from baseline to patient visit, 68.6%–48.6% [24-h LCIG] and 75.1%–70.2% [16-h LCIG]) (Fig. 1A and Supplemental Table 1). There were reductions in prevalence of nocturnal/morning akinesia with both 24-h and 16-h LCIG (−42.9% and −19.4%). While both groups showed an increase in dysphagia prevalence from baseline to patient visit (24-h LCIG, 5.7%; 16-h LCIG, 7.7%), the increase was smaller with 24-h LCIG. Balance problems showed the opposite effect, with 24-h LCIG showing a small increase and 16-h LCIG showing a small decrease (2.9% vs −2.7%) (Fig. 1A). Similarly, reductions were evident for within-group changes from baseline for severity and frequency of most motor symptoms for both 24-h and 16-h LCIG (Supplemental Figs. 2A and B; Supplemental Table 1). More pronounced reductions were identified in severity and frequency of freezing of gait with 24-h versus 16-h LCIG ($p = 0.012$ and $p = 0.038$; Supplemental Figs. 2A and B).

3.2.2. NMS and treatment-related symptoms

While pain was higher for patients in 24-h LCIG group at baseline, no difference between groups was found at patient visit (Supplemental Table 2). There were reductions from baseline in prevalence of some NMS with 24-h and 16-h LCIG, including anxiety, pain, depression, constipation, and fatigue (24-h LCIG only) (Fig. 1B). Changes from baseline were significantly different for severity of urinary symptoms (day and night) and frequency of cognitive impairment with 24-h versus 16-h LCIG ($p = 0.006$ and $p = 0.014$; Supplemental Figs. 2C and D). There were no differences between groups in prevalence, severity, or frequency of the change from baseline in treatment-related symptoms (Supplemental Figs. 3A, B, and C).

3.2.3. Add-on medications and LCIG parameters

At 12 months after LCIG initiation, LCIG monotherapy was greater with 24-h LCIG versus 16-h LCIG (% [n/N], 43.8% [14/32] vs 30.1% [102/339]; $p = 0.0300$). The mean number of add-on therapy intakes per day was reduced in both groups from baseline (mean ± SD, 10.8 ± 7.9 intakes for both groups) to 12 months after LCIG initiation (mean ± SD, 2.1 ± 1.3 and 2.4 ± 2.2 intakes with 24-h and 16-h LCIG). The percentage of patients receiving add-on medications decreased for both treatment groups over time (Supplemental Fig. 4).

Patients received 24-h LCIG for a mean ± SD duration of 806.1 ± 760.5 days (median [interquartile range], 702.0 [323.0, 1146.0]) (Supplemental Table 3). The mean ± SD total LCIG dose per day for 24-h infusion was 2260.9 ± 748.8 mg. Twenty-six patients (63.4%) required more than 2000 mg/day of LCIG. A total of 19 patients switched to 24-h LCIG after 16-h LCIG for mean ± SD treatment duration 13 ± 14.2 months (Supplemental Table 3). Mean ± SD total LEDD of LCIG increased from 2196.6 ± 942.7 mg at the last time point before the switch to 3322.6 ± 1323.4 at the patient visit (Supplemental Table 3).

There were 25 patients (62.5%) with 24-h LCIG who received a different LCIG dosage during daytime versus nighttime. The mean ± SD total dose ranged from 1332.9 ± 281.4 mg to 664.8 ± 289.6 mg, with a mean nighttime dose reduction of 51.3% ± 22.0. Mean daytime LCIG infusion duration was 15.6 ± 1.9 h/day and the nighttime LCIG infusion duration was 9.5 ± 3.3 h/day (Supplemental Table 3).

3.2.4. Regression analysis

Full description of regression analysis parameters can be found in Supplemental Table 4. Younger patients, patients with a lower number of motor symptoms, patients with longer duration "off" state times, patients with shorter dyskinesia state time, and patients with less severity of dyskinesia had an increased probability of being placed on 24-h LCIG.

3.2.5. Safety at LCIG initiation and LCIG maintenance treatment

AEs at LCIG initiation or during LCIG maintenance treatment were observed in 31.4% (n/N = 11/35) and 27.3% (n/N = 100/366) of patients with 24-h and 16-h LCIG (Supplemental Table 5). The most common AEs were stoma site discharge (24-h LCIG, n = 2, 5.7%; 16-h LCIG, n = 3, 0.8%) and pneumoperitoneum (24-h LCIG, n = 2, 5.7%; 16-h LCIG, n = 1, 0.3%). AEs of special interest included hallucinations (24-h LCIG, n = 1, 2.9%; 16-h LCIG, n = 3, 0.8%).

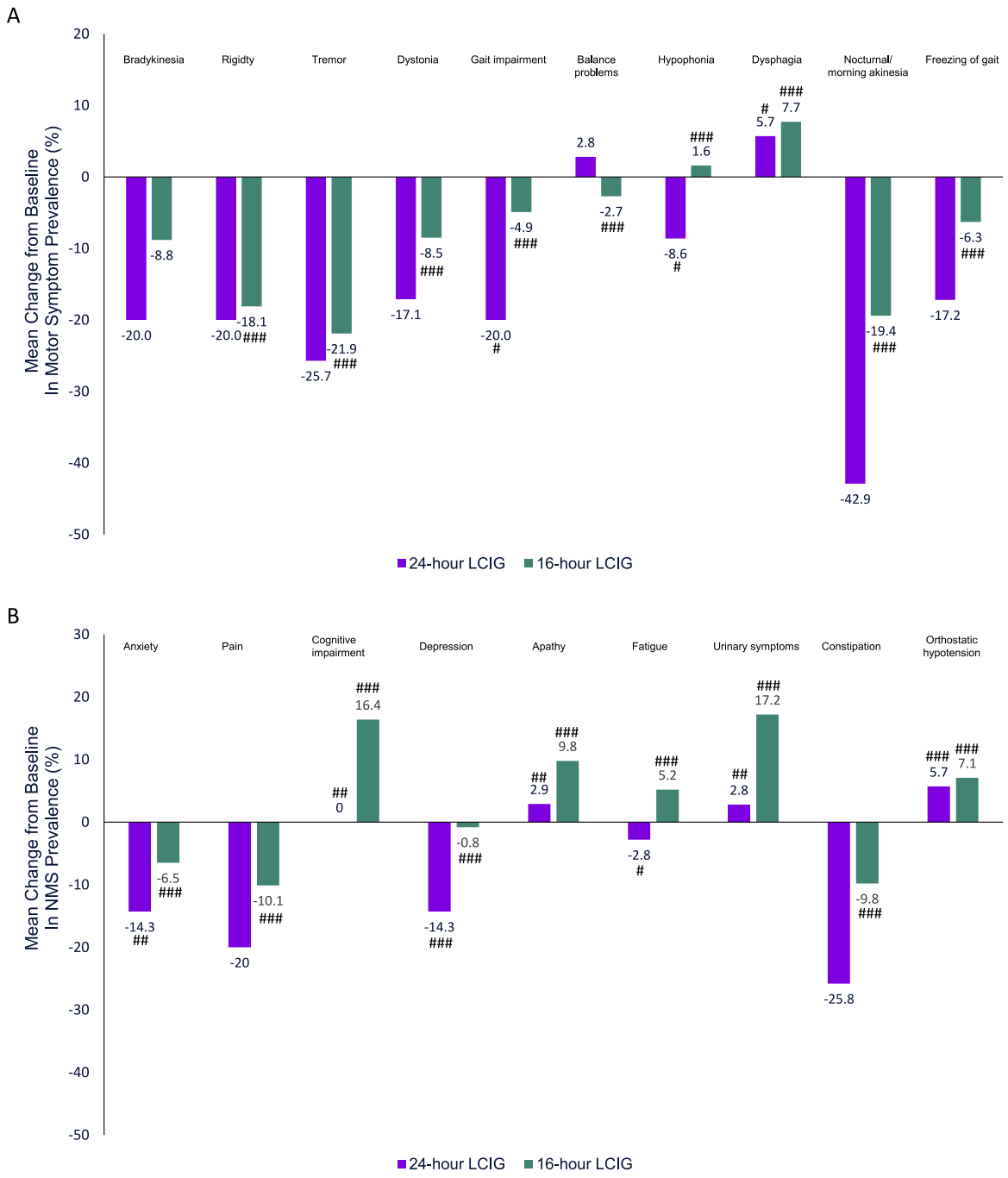

Fig. 1. Mean change from baseline in prevalence of motor symptoms (A) and NMS (B) in patients with 24-h or 16-h LCIG
LCIG, levodopa-carbidopa intestinal gel.
Within group differences, $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$.
Between group differences, $^{*}p < 0.05$; $^{**}p < 0.01$.

4. Discussion

LCIG reduced the incidence of motor symptoms and NMS in patients with APD. In patients with remaining symptoms, most motor symptoms and NMS were improved in severity and frequency with both 24-h LCIG and 16-h LCIG, some of which like urinary symptoms and cognitive impairment which showed greater improvement with 24-h LCIG versus 16-h LCIG. No differences were found between groups in change from baseline for off time, dyskinesia duration, or severity. Add-on therapy was reduced with both 24-h and 16-h LCIG. 24-h LCIG was more often prescribed to patients who had fewer motor symptoms, longer "off" state times, shorter dyskinesia state times, less severe dyskinesia, and/or were younger. Monotherapy was more common with 24-h versus 16-h LCIG. Both 24-h and 16-h LCIG were well-tolerated.

The current results align with others showing improvements in motor complications and NMS in PD with 24-h LCIG [9,18,19]. With 24-h LCIG, dyskinesia was significantly reduced across all 12 patients studied, daytime dyskinesia was reduced for 9 patients, and 2 reported improvement in freezing of gait [9]. Further, 24-h LCIG improved freezing of gait and reduced falls in patients who did not show freezing of gait improvements with levodopa [20,21]. Improvements in night-time symptoms, including sleep problems, have also been described [8,

13,19]. A recent review suggests patients with poorly controlled nocturnal symptoms would particularly benefit from 24-h LCIG [19]. Though others have reported an increased risk of psychotic symptoms with 24-h LCIG, there were no significant differences in hallucinations in the current study with 24-h versus 16-h LCIG [18].

The primary study limitations include the retrospective, post-hoc design, which did not allow for longitudinal analysis. Safety data were limited due to the retrospective chart review nature of the analysis. Additionally, statistical analysis was limited due to small group size for 24-LCIG and exploratory nature of this study. The levodopa equivalent daily dosage was greater with 24-h versus 16-h LCIG, making it difficult to separate the impact of overall dose from continuous dosing. Furthermore, patients with 24-h versus 16-h LCIG may have had a greater symptom burden at baseline. Initiation of 24-h LCIG was often based on nocturnal/morning akinesia and sleep problems. Likewise, a greater proportion of patients within the 24-h LCIG group had greater baseline values for uncontrolled dyskinesia, dystonia, dysphagia, and pain, versus those in the 16-h LCIG group. The distribution of patients to the 24-h LCIG group versus 16-h LCIG group for clinical reasons renders limited interpretation of the direct comparison of the 2 groups. Switching patients from 16-h LCIG to 24-h LCIG requires careful consideration and risk: benefit evaluation that is specific to each individual patient. Though interpretation of safety data was limited in this analysis, no differences were found between groups.

5. Conclusions

Both 24-h and 16-h LCIG led to improvement in specific motor symptoms, as well as NMS and treatment-related symptoms in patients with APD who were treated with LCIG for ≥12 months. Some improvements with LCIG were more pronounced with 24-h LCIG versus 16-h LCIG (eg, gait, urinary symptoms, and cognitive impairment). Safety findings were consistent within the known LCIG profile [8]. Both 24-h and 16-h LCIG are potential effective treatment options for patients with APD. Further investigation is required to understand how to identify patients who are suitable for the 24-h LCIG regimen in terms of weighing benefits versus risks.

Contributors

All authors had access to relevant data, and participated in the writing, review, and approval of the manuscript. NK contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. JS contributed in acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. LVD contributed in acquisition of data; critical revision of the manuscript for important intellectual content. PS contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. SF contributed in analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. JCP contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. OSS contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. LB contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision. TG contributed in acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision. AF contributed in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision.

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Declaration of competing interest

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Appendix A. Supplementary data

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