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Foslevodopa–Foscarbidopa Subcutaneous Infusion in Parkinson's Disease: A Cross-Cultural/Cross-Racial International Multicentre Comparative Tolerability Study (CRIM-FOS Study)

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Keywords:

Advanced Parkinson’s disease, Foslevodopa–Foscarbidopa.

Background:

Advanced Parkinson's disease (APD) often presents challenges such as irregular gastric absorption and delayed gastric emptying, leading to significant and unpredictable fluctuations in both motor and non-motor symptoms. Our study is a real-world, open-label study of the tolerability and efficacy of subcutaneous infusion of Foslevodopa/Foscarbidopa (FL/FC) focus on comparing White Caucasian patients and non-White patient cohorts

Methods

A database of 50 patients with APD across four international centers, for the FL/FC therapy program was examined and analysed for racial/ethnicity breakdown, motor, nonmotor and quality of life measures and tolerability using established criteria. . Participants underwent assessments at 6 and 12 months, making this one of the largest global cross-racial Caucasian (62%) and non-Caucasian patients (38%) Statistical analyses were performed using IBM SPSS Statistics version 31, with significance set at $p < 0.05$.

Results

In 50 patients (48% men , 38% of non-caucasian origin) with APD, Motor (UPDRS III) scores significantly declined from a baseline mean of 40.26 (SD = 10.21) to 24.84 (SD = 6.67) at 12 months ($p < .001$). Health-related quality of life, measured by the PDQ-8, improved significantly, with a mean difference of 6.11 ($p < .001$). The dropout rate was low at 10%, with an average time to dropout of 3 months (range: 2-4 months), primarily due to dose-limiting adverse effects like severe dyskinesias and financial constraints.

Conclusion:

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Subcutaneous infusion of FL/FC significantly improves motor function and sleep quality in advanced Parkinson's patients, reduces caregiver burden, enhances quality of life and effective across racial backgrounds. Our study underscores the importance of careful patient selection and monitoring during dose adjustments to optimize long-term outcomes.

Introduction:

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting approximately 1–2% of individuals over the age of 60 years[1, 2]. In Middle Eastern countries, the prevalence of PD varies significantly, ranging from 31.4 to 557.4 cases per 100,000 people [3]. A recent EmPark study by Metta et al. [4] emphasized the genetic diversity and distinct endophenotypes of PD within the United Arab Emirates (UAE) population, underscoring the critical need for early diagnosis and the optimal adjustment of dopaminergic therapy [4]; this study indicates that data from the UAE and other Middle Eastern countries may not accurately reflect the true burden of neurodegenerative conditions. This discrepancy is likely due to factors such as underdiagnosis, limited awareness, cultural influences, and the stigma associated with these disorders, as highlighted in another study by Alokley et al. (2024) [5]. Therefore, exploring the differences between Caucasian expats and non-Caucasian local Emirati populations, particularly in terms of motor function and variations in response to levodopa treatment, has become increasingly important.

Since the 1960s, levodopa (LD) has been regarded as the most effective symptomatic treatment for PD and is often referred to as a "miracle drug" because of its profound impact on both motor and non-motor symptoms in untreated patients. The oral administration of LD in combination with carbidopa (CD) is considered the gold standard for pharmacological treatment, particularly in the early stages of the disease [6].

The short plasma half-life of levodopa (LD) and inconsistent absorption from oral tablets, often due to impaired gastric motility, lead to fluctuating LD levels and complicate Parkinson's disease (PD) symptom management. Patients experience "ON" periods with effective symptom control and "OFF" periods with poor mobility, tremors, stiffness, and dyskinesias [7]. In advanced Parkinson's disease (APD), erratic gastric absorption and delayed gastric emptying exacerbate these fluctuations [8-11] and can lead to medication overload. Unpredictable "OFF" periods often make non-oral infusion therapies or Device-Aided Therapies (DAT)

necessary. Additionally, the high pill burden can lead to nonadherence to oral therapies, further indicating the need for DAT.[16-18]

To manage motor complications, patients often require higher doses and more frequent oral LD along with other medications, such as dopamine agonists, anticholinergics, amantadine, monoamine oxidase-B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors. These complex regimens increase the risk of drug interactions, can be burdensome for patients, and may lead to nonadherence because of the high pill burden [19-23]

A recent consensus initiative using a multi-country Delphi panel identified functional indicators of APD, which were validated in the OBSERVE-PD study [24]. This led to the creation of the 5-2-1 motor paradigm [25], which defines APD patients as those who require more than five oral levodopa doses per day, experience more than two hours of “OFF” symptoms daily, and have more than one hour of troublesome dyskinesia daily. This framework aids in identifying advanced patients and ensuring timely referrals for device-aided treatments.

To improve PD symptom control when oral medications are insufficient, non-oral, device-assisted therapies can be used for continuous treatment. Options include deep brain stimulation (DBS), levodopa/carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CSAI), which provide more stable symptom management and enhance quality of life [26].

Despite their effectiveness, many patients are hesitant to consider device-aided therapies because of the fear of surgery, potential complications, cosmetic concerns, and side effects. Furthermore, limited access to specialized centres and the inconsistent application of international guidelines for APD treatments hinder patient acceptance and access. For instance, DBS is generally not recommended for elderly patients or those with dementia or psychotic disorders [27,28]. Similarly, the effectiveness of CSAI may be limited by progressive efficacy loss and reduced absorption due to panniculitis [29,30]. While LD is the standard treatment for PD because of its efficacy and safety, the benefits of continuous delivery methods such as LCIG are diminished by the need for surgical intervention [31]. These challenges highlight the urgent need for non-surgical treatment options that can provide stable LD plasma concentrations and continuous symptom relief for patients with APD.

Foslevodopa/foscarbidopa (FL/FC) is a novel soluble formulation of levodopa (LD)/carbidopa (CD) prodrugs for treating PD; it is delivered via CSCI using a portable pump, allowing 24-hour administration [32-33]. This formulation rapidly converts to active LD and CD. Phase 1 studies have revealed that CSCI effectively maintains consistent plasma levels of LD, addressing the diverse needs of patients with APD. In a 12-week phase 3 study, compared with oral immediate-release LD/CD, FL/FC significantly improved motor fluctuations, indicating its potential as a more effective treatment option [32].

To enhance personalized medicine for Parkinson's disease patients, data on the use of drugs need to be reported for different communities, races and cultures, as responses may vary substantially owing to personality, cultural and pharmacogenetic issues [34,35]. Most of the data concerning the use of investigational medical products are based on White western Caucasian cohorts, underpinning a major cause of health data inequity. Our study is the first to report the comparative efficacy and tolerability of FL/FC in a non-white Emirati cohort and a White Caucasian comparator cohort. Doubling of PD rates in the UAE and Asia is predicted by 2040, and the data from our study are therefore likely to have widespread societal and medical implications for the UAE.

Objectives:

This was a pragmatic real-life, open-label, world-first, cross-racial study comparing the efficacy and tolerability of FL/FC in Emirati-Asian and White Caucasian PD cohorts. Data from the Parkinson's Centre of Excellence at Kings College Hospital Dubai, UAE, Bahrain Speciality Hospital, Bahrain, Poznan Parkinson's Centre, Poland and Lund University Hospital, Lund, Sweden, were combined and analysed. Ethnicity in all the subjects was recorded using established criteria [36].

The key objectives were as follows:

- To establish tolerability rates for FL/FC in White Caucasian cohorts and non-white cohorts (Arab/Emirati-Asian subjects at 6 and 12 months);
- Concurrently address the comparative efficacy of FL/FC in white and Emirati-Asian subjects in relation to motor symptoms, non-motor symptoms, sleep, pain, carer burden, hospital admission, and quality of life; and

- Document side effects and confounders, such as body mass index (BMI), that evolved from baseline to 6 months and 12 months.

Methods:

Accordance statement:

All the methods and procedures were performed in accordance with relevant guidelines and regulations. Bonferroni correction was applied within repeated-measures contrasts, and the Limitations section highlighting issues regarding multiple endpoints and exploratory interaction analyses was strengthened.

Patient Consent:

Informed consent was obtained from all the participants.

Participants:

Fifty patients with APD were enrolled from four international centres: King's College Hospital London Dubai, Bahrain Specialty Hospital, University Hospital of Poznan in Poland, and Lund in Sweden. A database was generated for patients participating in the FL/FC therapy program, allowing the creation of a diverse and comprehensive cross-racial global comparative cohort. Participants completed assessments at 6 and 12 months. Eligibility for participation was based on local guidelines and the general 5-2-1/Manage PD criteria for initiating FL/FC. [37]

Inclusion Criteria:

1. Age ≥ 18
2. Clinical diagnosis of PD per MDS criteria
3. ≥ 2.5 hours OFF time daily prior to initiation
4. Stable PD medications for ≥ 30 days prior to enrolment
5. Recognizable ON/OFF states
6. DBS or apomorphine therapy was allowed if the patient was stable.
7. Able to provide informed consent
8. Able commit to the 12-month study
9. Had caregiver support

Exclusion Criteria:

1. Hoehn and Yahr (H&Y) stage V and institutionalization
2. Pregnant or nursing

3. Conditions interfering with assessments (e.g., dementia and Mini-Mental State Examination (MMSE) score < 21).

Procedures and Assessments:
Data were collected using routine clinical assessments. Ethnicity was recorded using established UK criteria (as above).

Patient-Based Measures:

- Demographics (age, sex, race, duration of disease, BMI, etc.)
- Non-Motor Symptom Questionnaire (NMSQ)
- Parkinson's Disease Sleep Scale (PDSS)
- Epworth Sleepiness Scale (ESS)
- Parkinson's Disease Questionnaire-8 (PDQ-8)
- Zarit Caregiver Burden Interview (ZCBI)

Investigator-Based Measures:

- Hoehn and Yahr (H & Y) stage
- Unified Parkinson's Disease Rating Scale (UPDRS) parts 3/4
- King's Parkinson's Disease Pain Scale (KPPS)

Other Data:

- Levodopa equivalent daily dosage (LEDD) [39]

Assessment Details

All the instruments have been validated for PD and have been successfully used in many previous studies.

- H&Y classification is widely used to establish PD stage. The original HY scale was adopted in this study [40].

- The UPDRS part III is a 33-item valid motor measure of PD. Possible responses range from 0 (normal) to 4 (severe), and the total score ranges between 0 and 132 [41].

- The UPDRS part IV is a valid motor measure of medication complications (dyskinesias). Possible responses range from 0 (normal) to 4 (severe), and the total score ranges between 0 and 24 [41].

- The NMSQ is composed of 30 items grouped into nine nonmotor domains. Each item is scored as “yes” or “no”, and the total score ranges between 0 and 30 [42].

- The ESS is a subjective measure of a patient’s sleepiness. The total score ranges from 0 to 24 [43].

- The PDSS-2 is a self-rating questionnaire composed of 15 items about various sleep and nocturnal disturbances. The total score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance) [44].
- The PDQ-8 is an 8-item instrument that specifically assesses the health-related quality of life of PD patients [45].
- The Zarit Caregiver Burden Interview (ZCBI) is a comprehensive 22-item scale designed to assess caregiver burden [46].
- The Kings Parkinson Pain Scale (KPPS) consists of 14 items organized into seven domains corresponding to seven subtypes of pain. Severity (on a scale of 0–3) and frequency (on a scale of 0–4) are measured, and the total score ranges between 0 and 168[47].

Safety Monitoring:

Adverse events (AEs) and serious adverse events (SAEs) were documented with regard to onset, duration, severity, outcome, and causality. An independent oversight committee addressed the occurrence of AEs.

Ethical Considerations:

All the participants underwent neurological evaluations and specific assessments for PD conducted by qualified health care professionals. This study received ethics approval from the Dubai Scientific Research Ethics Committee and King's College Hospital in Dubai (REC/K21(2025)). This study was also carried out in compliance with the General Data Protection Regulation (GDPR) as endorsed by the UAE Parkinson's expert group and the Parkinson's Association (UAE). Patients recruited for the study were invited to attend a baseline visit for assessments alongside their caregivers. Caregivers were required to provide informed consent and maintain regular contact with the patient for a minimum of 20 hours per week.

Statistical analysis:

Statistical analyses were conducted using IBM SPSS Statistics version 31, with significance set at a two-sided p value of less than 0.05. Baseline characteristics and tolerability outcomes are summarized with descriptive statistics: continuous variables are presented as the mean and standard deviation or median with interquartile range, and categorical variables are presented as counts and percentages. Between-group comparisons at

baseline were performed using Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables, with Fisher's exact test used when necessary. Longitudinal changes in clinical outcomes for treatment completers were analysed using repeated-measures ANOVA, with time as a within-subject factor and race/ethnicity as a between-subject factor. Mauchly's test was used to assess sphericity; Greenhouse–Geisser corrections were applied when necessary. The main effects of time, interactions between time and race, and race effects were evaluated, with effect sizes reported as the partial eta squared for significant findings. Bonferroni-adjusted pairwise comparisons were used to analyse changes between the baseline, 6-month, and 12-month assessments, interpreting mean differences based on the direction of change over time. Spearman rank-order correlation analyses were performed to assess the associations between FL/FC 24-hour infusion doses and motor outcomes at follow-up for the overall cohort and by race, with 95% confidence intervals estimated using Fisher transformation.

Demographics:

Fifty patients with APD were enrolled across four international centres. The cohort included 24 men (48.0%) and 26 women (52.0%). Thirty-one patients (62.0%) were classified as Caucasian, and 19 (38.0%) were classified as non-Caucasian (15 individuals of Arabic descent and 4 individuals of Asian descent, specifically Indian, Filipino, Indian, and Pakistani origins). The mean age at the initiation of FL/FC infusion was 66.80 years (*SD* = 8.66), with a median age of 67.50 years (interquartile range 60.00 to 72.00). The mean body weight was 61.20 kg (*SD* = 8.64), and the mean body mass index was 23.88 kg/m² (*SD* = 3.61). The PD phenotype was predominantly akinetic-rigid (*n* = 26, 52.0%), followed by tremor-dominant (*n* = 15, 30.0%) and mixed (*n* = 9, 18.0%) presentations. The mean disease duration at baseline was 11.28 years (*SD* = 4.11), with a median duration of 10.00 years (interquartile range 8.00 to 15.00). Disease severity at treatment initiation was relatively uniform, with a mean H&Y stage of 3.12 (*SD* = 0.31) (Table 1)

Table 1: Baseline Characteristics and Tolerability by Treatment Discontinuation Status

Variables	Treatment Discontinuation Status		
	Completers (n = 43)	Discontinuers (n = 7)	p value
Gender, *n* (%)			.697
Male	20 (46.5)	4 (57.1)	
Female	23 (53.5)	3 (42.9)	
Race/Ethnicity, *n* (%)			1.00
Caucasians	27 (62.8)	4 (57.1)	
No Caucasians	16 (37.2)	3 (42.9)	
Age, *years*	66.05 ± 8.91; 67 (60–72)	71.43 ± 5.29; 69 (67–79)	.130
Weight, *kg*	62.14 ± 8.46; 64 (59–70)	55.43 ± 7.96; 52 (50–67)	.066
Body Mass Index, *kg/m²*	24.42 ± 3.57; 25 (21–27)	20.57 ± 1.40; 20 (19–22)	.010
Parkinson's Disease Type, *n* (%)			.206
Tremor-Dominant	12 (27.9)	3 (42.9)	
Akinetic-Rigid	22 (51.2)	4 (57.1)	
Mixed	9 (20.9)	0 (0.0)	
Disease Duration, *years*	11.84 ± 4.14; 12 (8–15)	7.86 ± 1.35; 8 (6–9)	.016
H&Y Stage	3.13 ± 0.33; 3 (3–3)	3.07 ± 0.19; 3 (3–3)	.826
Baseline oral LED, mg	1140 ± 466; 1100 (900–1400)	1086 ± 90; 1100 (1000–1200)	.801
FL/FC 24-h dose (baseline)	0.28 ± 0.06; 0.29 (0.25–0.30)	0.26 ± 0.09; 0.20 (0.20–0.35)	.304
FL/FC 24-h dose (6 months)	0.35 ± 0.05; 0.35 (0.30–0.40)	0.32 ± 0.03; 0.30 (0.30–0.35)	.149
Skin reaction AE, n (%)	8 (18.6)	3 (42.9)	.170
Hallucinations AE, n (%)	8 (18.6)	3 (42.9)	1.00
Psychosis AE, n (%)	5 (11.6)	1 (14.3)	1.00
Dystonic pain, n (%)	–	2 (28.6)	
Severe dyskinesias, n (%)	–	4 (57.1)	
Time to dropout, months	–	3 (2–4)*	

Note: Continuous variables are reported as mean ± standard deviation and median (interquartile range: Q1–Q3); categorical variables are presented as n (%). Between group comparisons were conducted using the Mann–Whitney U test for continuous variables. For categorical variables, Fisher's exact test was applied when expected cell counts were below 5; otherwise, the (†) Chi-square test was used. Treatment discontinuation was defined as cessation of Foslevodopa–Foscarbidopa infusion prior to completion of the 12-month follow-up. Time to treatment discontinuation is reported for treatment discontinuers only.

Tolerability & Infusion dosing regimen:

A repeated-measures ANOVA was performed to assess changes in FL/FC 24-hour infusion doses over time (baseline, 6 months, and 12 months) and to determine whether these changes differed by race (Caucasian vs. non-Caucasian) among 43 treatment completers. The mean dose increased over the follow-up period (baseline M = 0.28, SD = 0.06; 6 months M = 0.35, SD = 0.05; 12 months M = 0.41, SD = 0.06). Mauchly's test showed a violation of sphericity for time (W =

0.45, p < .001); thus, Greenhouse–Geisser corrected results are presented. There was a significant main effect of time [F (1.29, 52.87) = 99.87, p < .001, partial η^2 = .71]. Bonferroni-adjusted comparisons revealed significant dose increases from baseline to 6 months (mean diff = −0.07, p < .001), from baseline to 12 months (mean diff = −0.13, p < .001), and from 6 to 12 months (mean diff = −0.06, p < .001). A significant main effect of race was also found [F (1, 41) = 4.39, p = .042, partial η^2 = .10], indicating lower average doses in non-Caucasian patients (0.33) than in Caucasian patients (0.36). The time × race interaction was significant [F (1.29, 52.87) = 4.90, p = .023, partial η^2 = .11], suggesting different dose trajectories by race. At baseline, non-Caucasian patients received a lower mean dose than Caucasian patients (non-Caucasian M = 0.25, SD = 0.04; Caucasian M = 0.30, SD = 0.06). However, by 12 months, the mean doses were similar for both groups (non-Caucasian M = 0.41, SD = 0.06; Caucasian M = 0.41, SD = 0.07). Bonferroni-adjusted comparisons revealed significant increases in doses over time for both groups: non-Caucasian patients (baseline vs. 6 months: mean difference = -0.08, p < .001; baseline vs. 12 months: -0.16, p < .001; 6 vs. 12 months: -0.08, p < .001) and Caucasian patients (baseline vs. 6 months: -0.06, p < .001; baseline vs. 12 months: -0.10, p < .001; 6 vs. 12 months: -0.05, p = .002). Dystonic pain and severe dyskinesias reported by treatment discontinuers occurred during the titration phase following the initiation of foslevodopa–foscarbidopa infusion. (Table 2) These events were considered dose-limiting adverse effects rather than stable pre-existing symptoms that failed to resolve.

Table 2: *Changes in Foslevodopa–Foscarbidopa 24-Hour **Infusion Dose** Over Time According to Race*

Outcome	Group	Baseline	6 Months	12 Months	Time p	Time × Race p
FL/FC 24-hour infusion dose	Total	0.28 ± 0.06	0.35 ± 0.05	0.41 ± 0.06	<.001	.023
	Caucasian	0.30 ± 0.06	0.36 ± 0.06	0.41 ± 0.07		
	Non-Caucasian	0.25 ± 0.04	0.33 ± 0.04	0.41 ± 0.06		

Note: Data are mean ± SD for treatment completers (n = 43). Repeated-measures ANOVA was used with Time as the within-subject factor and Race as the between-subject factor. Greenhouse–Geisser correction was applied when sphericity was violated. Reported p values refer to the main effect of Time and the Time × Race interaction. FL/FC indicates Foslevodopa–Foscarbidopa

Longitudinal Efficacy Outcomes (Motor Outcomes):

Repeated-measures ANOVA was conducted to assess changes in motor function (UPDRS III) and dyskinesia severity (UPDRS IV) across time (baseline, 6 months,

and 12 months) and to assess whether trajectories differed by race (Caucasian vs. non-Caucasian) among treatment completers. We opted to use the older UPDRS [41] instead of the MDS-UPDRS, as it is the local pathway measure preferred in our clinic due to time constraints.

The mean UPDRS III score decreased over time in the overall cohort (baseline M = 40.26, SD = 10.21; 6 months M = 27.77, SD = 6.98; 12 months M = 24.84, SD = 6.67). Mauchly's test indicated a violation of sphericity (W = .274, p < .001); therefore, Greenhouse–Geisser corrected results are reported. There was a significant main effect of time [F(1.16, 47.52) = 97.61, p < .001, partial η^2 = .70]. Bonferroni-adjusted pairwise comparisons revealed significant improvements from baseline to 6 months (mean difference = 11.59 points, p < .001), from baseline to 12 months (mean difference = 14.33 points, p < .001), and from 6 to 12 months (mean difference = 2.74 points, p < .001). A secondary between-subjects main effect of race was observed for the average UPDRS III score across time [F (1, 41) = 4.23, p = .046, partial η^2 = .09], with higher overall motor scores in non-Caucasian patients than in Caucasian patients. The time × race interaction was also statistically significant [F (1.16, 47.52) = 8.76, p = .003, partial η^2 = .18], indicating differential motor improvement trajectories between race groups. Within-group Bonferroni-adjusted comparisons demonstrated significant improvements across all time contrasts in both groups (p < .001); however, the magnitude of improvement was greater among Caucasian patients. From baseline to 12 months, the mean UPDRS III score decreased by 18.59 points among Caucasian patients and by 10.06 point among non-Caucasian patients. Improvements from 6 to 12 months were also greater in Caucasian patients (3.48 vs. 2.00 points). At baseline, mean UPDRS III scores were comparable between groups, whereas at 6 and 12 months, compared with non-Caucasian patients, Caucasian patients had lower mean scores. (Table 3)

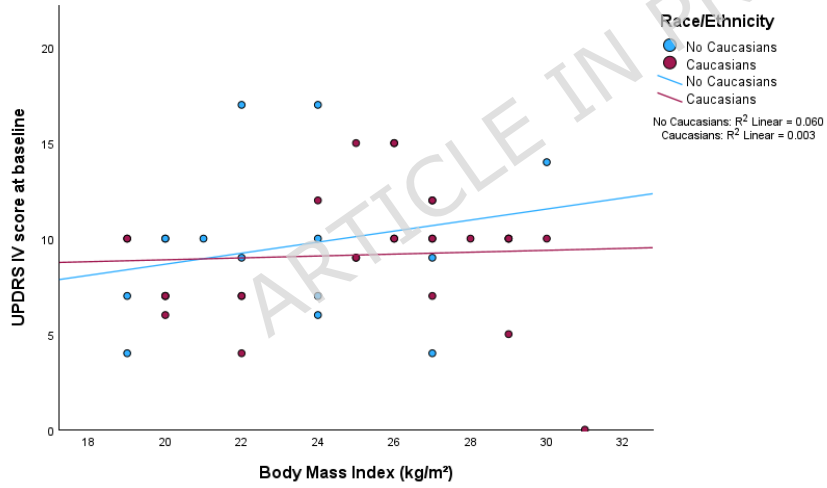
Table 3: *Changes in Motor Complications and Motor Severity Over Time According to Race (UPDRS Part III and Part IV)*

Outcome	Group	Baseline	6 Months	12 Months	Time p	Time × Race p
UPDRS	Total	40.26 ± 10.21	27.77 ± 6.98	24.84 ± 6.67	< .001	.003
III	Caucasian	40.59 ± 11.33	25.48 ± 6.00	22.00 ± 4.68		
	Non-Caucasian	39.69 ± 8.29	31.63 ± 6.97	29.63 ± 6.91		
UPDRS	Total	9.30 ± 3.52	9.56 ± 6.00	11.14 ± 6.32	.085	.385
IV	Caucasian	9.15 ± 3.32	8.78 ± 6.77	10.11 ± 6.65		
	Non-Caucasian	9.56 ± 3.93	10.88 ± 4.27	12.87 ± 5.49		

Note: Data are mean ± SD for treatment completers (n = 43). Repeated-measures ANOVA was used with Time as the within-subject factor and Race as the between-subject factor. Greenhouse–Geisser correction was applied when sphericity was violated. Reported p values refer to the main effect of Time and the Time × Race interaction. UPDRS III indicates Unified Parkinson's Disease Rating Scale Part III (motor examination); UPDRS IV indicates Unified Parkinson's Disease Rating Scale Part IV (dyskinesias and motor complications).

The mean UPDRS IV scores in the overall cohort showed a modest increase over time (baseline M = 9.30, SD = 3.52; 6 months M = 9.56, SD = 6.00; 12 months M = 11.14, SD = 6.32). Bonferroni-adjusted pairwise comparisons revealed a significant increase in UPDRS IV scores between 6 and 12 months, with a mean difference of 1.67 points (p = .002). However, the changes observed from baseline to 6 months and from baseline to 12 months did not reach statistical significance. Additionally, the Time × Race interaction for UPDRS IV was not statistically significant F (1.25, 51.11) = 0.85, p = .385), suggesting that the trajectories of dyskinesia were similar across different racial groups over time. Additionally, in the overall cohort, a higher body mass index was significantly linked to lower UPDRS Part IV scores. This suggests that a lower body mass index is associated with a higher risk of dyskinesias.(Fig 1)

Figure 1: Association between Body Mass Index and UPDRS Part IV score at baseline, stratified by race



Note: Points represent individual patients. Solid lines indicate fitted linear trends within each race group. Blue markers and line denote non-Caucasian patients, and red markers and line denote Caucasian patients. In the overall cohort, higher body mass index was significantly associated with lower UPDRS Part IV scores at bas

Longitudinal Efficacy (Non-Motor outcomes):

Overall Non-Motor Symptom Burden:

Our study revealed no significant overall change in total NMSQ score over time. However, there was a significant interaction between time and race, indicating different trends for racial groups. For non-Caucasian patients, there was a significant increase in the NMSQ score from 6 to 12 months, whereas for Caucasian

patients, there were no significant changes. At 12 months, non-Caucasian patients had higher NMSQ scores (13.00) than Caucasian patients (8.96). Additionally, a significant main effect of race was observed, with non-Caucasian patients having higher overall NMSQ scores.

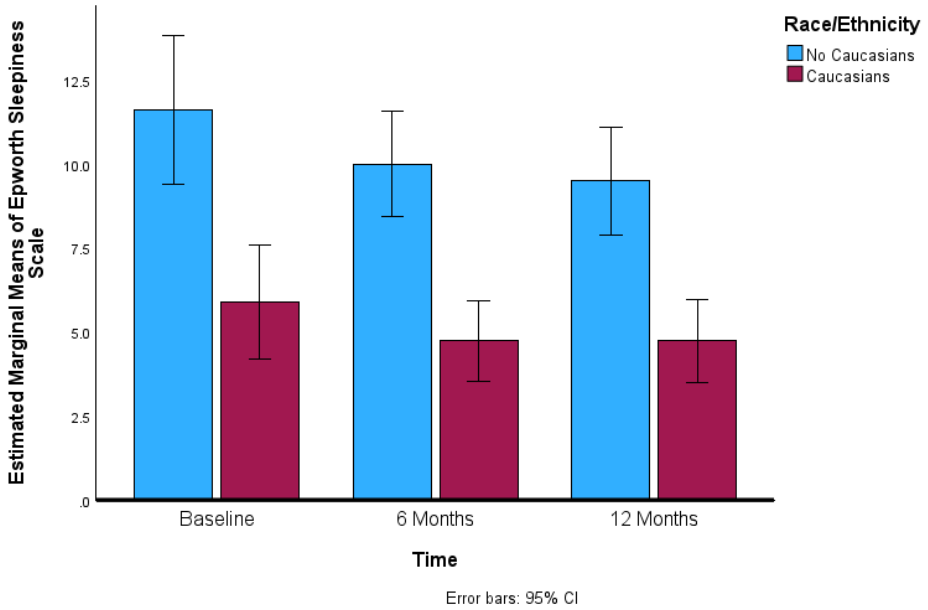
Health-related quality of life using the PDQ-8:

Our study assessed health-related quality of life using the PDQ-8. The results revealed significant improvement from baseline to 6 months (mean difference = 4.31, p < .001), from baseline to 12 months (mean difference = 6.11, p < .001), and from 6 to 12 months (mean difference = 1.79, p < .001). There was no significant interaction between time and race (F (1.44, 59.02) = 1.68, p = .200)

PDSS:

The mean PDSS score increased markedly over time, indicating improved sleep quality (baseline $M = 67.21$, $SD = 14.69$; 6 months $M = 86.63$, $SD = 22.36$; 12 months $M = 87.33$, $SD = 18.95$). The main effect of time was statistically significant [$F(1.42, 58.04) = 74.67$, $p < .001$, partial $\eta^2 = .65$]. Bonferroni-adjusted comparisons revealed significant improvements from baseline to 6 months (mean difference = −18.52, $p < .001$) and from baseline to 12 months (mean difference = −19.58, $p < .001$), with no significant change between 6 and 12 months. The time × race interaction was not statistically significant [$F(1.42, 58.04) = 1.93$, $p = .166$].(Fig 2)

Figure 2: Bar plot of the interaction between Time and Race on Epworth Sleepiness Scale scores



Note: The Time × Race interaction was not statistically significant (p = .319). Bars represent estimated marginal means by race; error bars indicate 95% confidence intervals. Blue bars denote non-Caucasian patients, and burgundy bars denote Caucasian patients

Bonferroni-adjusted pairwise comparisons indicated significant reductions in ESS scores from baseline to 6 months (mean difference = 1.39, $p = .004$) and from baseline to 12 months (mean difference = 1.64, $p < .001$), whereas the change from 6 to 12 months was not statistically significant. **T**he time × race interaction was not significant [F (1.10, 45.11) = 1.05, $p = .319$]; however, a significant between-subjects main effect of race was present [F (1, 41) = 24.23, $p < .001$, partial $\eta^2 = .37$], with higher ESS scores among non-Caucasian patients across time.

Bonferroni-adjusted pairwise comparisons indicated significant reductions in ESS scores from baseline to 6 months (mean difference = 1.39, $p = .004$) and from baseline to 12 months (mean difference = 1.64, $p < .001$), whereas the change from 6 to 12 months was not statistically significant. The Time × Race interaction was not significant, F (1.10, 45.11) = 1.05, $p = .319$; however, a significant between-subjects main effect of Race was present, F (1, 41) = 24.23, $p < .001$, partial $\eta^2 = .37$, with higher ESS scores among non-Caucasian patients across time (table 4)

Table 4: *Changes in Non-Motor Symptoms, Health-Related Quality of Life, Sleep, and Daytime Sleepiness Over Time According to Race*

Outcome	Group	Baseline	6 Months	12 Months	Time p	Time × Race p
NMSQ	Total	11.44 ± 4.15	10.14 ± 2.59	10.47 ± 3.55	.134	.012
	Caucasian	11.15 ± 4.70	10.26 ± 2.99	8.96 ± 2.70		
	Non-Caucasian	11.94 ± 3.07	9.94 ± 1.77	13.00 ± 3.44		
PDQ-8	Total	17.81 ± 7.96	13.63 ± 6.31	11.95 ± 5.92	< .001	.200
	Caucasian	13.44 ± 6.28	9.63 ± 4.07	8.30 ± 3.57		
	Non-Caucasian	25.19 ± 4.05	20.38 ± 2.33	18.13 ± 3.38		
PDSS	Total	67.21 ± 14.69	86.63 ± 22.36	87.33 ± 18.95	< .001	.166
	Caucasian	72.59 ± 10.23	94.63 ± 15.45	94.26 ± 15.43		
	Non-Caucasian	58.13 ± 16.82	73.13 ± 26.00	75.63 ± 18.96		
ESS	Total	8.02 ± 5.16	6.70 ± 4.00	6.51 ± 3.91	< .001	.319
	Caucasian	5.89 ± 5.29	4.74 ± 3.82	4.74 ± 3.82		
	Non-Caucasian	11.63 ± 1.96	10.00 ± 1.03	9.50 ± 1.51		

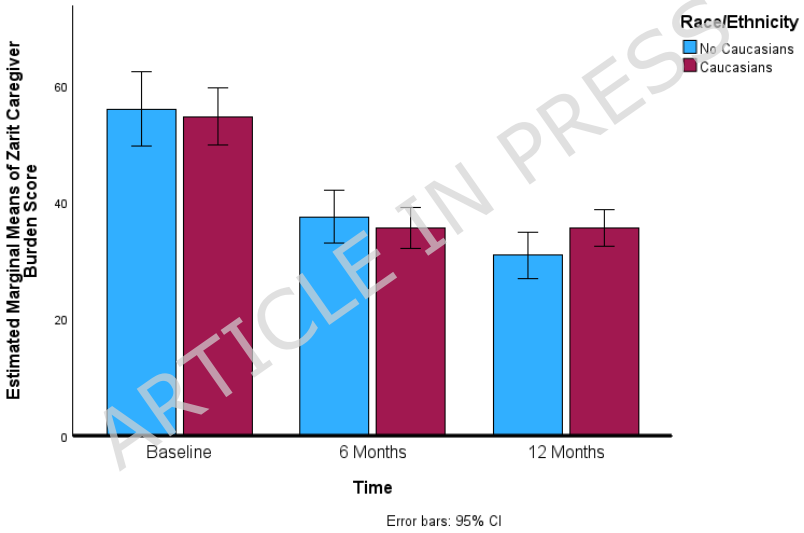
Note: Data are mean ± SD for treatment completers (n = 43). Repeated-measures ANOVA was used with Time as the within-subject factor and Race as the between-subject factor. Greenhouse–Geisser correction was applied when sphericity was violated. Reported p values refer to the main effect of Time and the Time × Race interaction. NMSQ indicates Non-Motor Symptoms Scale; PDQ-8 indicates

Parkinson's Disease Questionnaire-8 (health-related quality of life); PDSS indicates Parkinson's Disease Sleep Scale; ESS indicates Epworth Sleepiness Scale

The main effect of time was highly significant for caregiver burden:

Bonferroni-adjusted pairwise comparisons revealed significant reductions in caregiver burden from baseline to 6 months (mean difference = 18.77, $p < .001$), from baseline to 12 months (mean difference = 22.09, $p < .001$), and from 6 to 12 months (mean difference = 3.31, $p < .001$). The time × race interaction was also significant [F (1.41, 57.61) = 5.62, p = .012, partial η^2 = .12]. Within-race comparisons demonstrated continued reductions in caregiver burden from 6 to 12 months among non-Caucasian patients (mean difference = 6.63, p < .001), whereas caregiver burden plateaued between 6 and 12 months among Caucasian patients.(Fig 3)

Figure 3: Bar plot of the interaction between Time and Race on Zarit caregiver burden scores



Note: The Time × Race interaction was statistically significant (p = .012). Bars represent estimated marginal means by race; error bars indicate 95% confidence intervals. Blue bars denote non-Caucasian patients, and burgundy bars denote Caucasian patients

24-Hour Infusion vs. 12-hour Infusion:

Comparative interpretation of clinical benefits between the 12-hour and 24-hour infusion regimens:

We sought to determine whether patients on a 12-hour infusion schedule experience comparable or potentially greater benefits than those on a 24-hour regimen. However, only five patients (10%) transitioned to the shorter infusion schedule, primarily because of cost considerations. Notably, comparing the effectiveness of the two infusion schedules was not the intended objective of this

study. It is difficult to draw conclusions about the relative efficacy of the two regimens, with one being the standard recommendation (24 hours) and the other being a modified approach to accommodate patient needs (12 hours) because the five patients switched to a 12-hour infusion schedule to reduce financial strain and discomfort from overnight infusions (required for the 24-hour regimen), leading to the use of alternative treatments such as extended-release levodopa or transdermal rotigotine patches.

Clinical outcomes at 6 and 12 months were compared between patients who switched from a 24-hour to a 12-hour FL/FC infusion by the 12-month visit (n = 5) and those who continued with the continuous 24-hour infusion throughout the follow-up period (n = 38). The differences in score changes between the groups were analysed using Mann–Whitney U tests.A comparison of motor severity scores (UPDRS part III) among patients who received infusions with different durations revealed that the median change in UPDRS Part III scores from 6 to 12 months was 0.00 (IQR: −2.00 to 0.00) for those on the 12-hour infusion and −3.50 (IQR: −5.00 to 0.00) for those on the 24-hour infusion, suggesting better motor improvement in the latter group. However, this difference was not statistically significant (U = 62.00, z = −1.30, p = .194).

Similarly, there were no significant differences in UPDRS Part IV scores between the two groups during the same period, with both groups showing a median change of 0.00 (IQR: 0.00 to 3.00), leading to a nonsignificant result (U = 85.50, z = −0.42, p = .678). In a comparison of the groups during the 6- to 12-month period, non-motor symptom burden significantly differed between the patient groups. For those who switched to the 12-hour infusion, median increase in the NMSS score was 6.00 points, indicating worsening non-motor symptoms, whereas for patients on the 24-hour infusion, NMSS scores were stable; this difference was statistically significant (U = 19.50, z = −2.95, p = .003). Additionally, health-related quality of life improved in the 12-hour infusion group, with a median reduction of 6.00 points in the PDQ-8 score, while in the 24-hour group, there was no change.

The change in PDQ-8 scores was statistically significant [U = 30.50, z = −2.65, and p = .008]. However, no significant differences were found between the groups regarding sleep-related outcomes. The median change in PDSS scores from 6 to 12 months was 0.00 (IQR: 0.00 to 10.00) for patients on the 12-hour infusion and

0.00 (IQR: 0.00 to 0.00) for those on the 24-hour infusion (U = 59.00, z = −1.73, p = .084). For the ESS scores, for both groups, the median change was 0.00 (12-hour group IQR: −2.00 to 0.00; 24-hour group IQR: 0.00 to 0.00). While a statistical test suggested a difference (U = 60.00, z = −3.00, p = .003), the actual changes were minimal in both groups. The study revealed no significant differences in pain or caregiver burden between patients on the 12-hour and 24-hour infusion regimens over the 6- to 12-month period. The median change in the KPPS was 0.00 for both groups, and the change in the Zarit caregiver burden score was also similar, with minimal differences. Additionally, hospital admission rates were comparable for the two infusion regimens. (Table 5)

Overall, patients who switched to a 12-hour infusion regimen showed improvements in motor severity similar to those on a continuous 24-hour infusion for 6 to 12 months. However, the 12-hour group experienced worse non-motor symptoms and reported worse health-related quality of life, as indicated by lower NMSQ scores.

Table 5: Six- to Twelve-Month Changes in Clinical Outcomes by Infusion Regimen During Follow-up

Outcome (Δ12–6)	24-hour to 12-hour infusion transition (n = 5)	Continuous 24-hour infusion (n = 38)	p-values
UPDRS III (Δ12–6)	−1.40 ± 2.19; 0.00 (−2.00 to 0.00)	−3.13 ± 2.76; −3.50 (−5.00 to 0.00)	.194
UPDRS IV (Δ12–6)	2.00 ± 3.08; 0.00 (0.00 to 3.00)	1.53 ± 2.80; 0.00 (0.00 to 3.00)	.678
NMSQ (Δ12–6)	6.60 ± 5.08; 6.00 (4.00 to 10.00)	−0.50 ± 3.09; 0.00 (−2.00 to 0.00)	.003
PDQ-8 (Δ12–6)	−5.20 ± 3.63; −6.00 (−6.00 to −4.00)	−1.21 ± 1.44; 0.00 (−2.00 to 0.00)	.008
PDSS (Δ12–6)	6.00 ± 8.94; 0.00 (0.00 to 10.00)	0.00 ± 7.71; 0.00 (0.00 to 0.00)	.084
ESS (Δ12–6)	−1.00 ± 1.41; 0.00 (−2.00 to 0.00)	−0.08 ± 0.49; 0.00 (0.00 to 0.00)	.003
KPPS (Δ12–6)	−4.00 ± 5.48; 0.00 (−10.00 to 0.00)	−1.58 ± 3.70; 0.00 (0.00 to 0.00)	.196
Hospital admissions (Δ12–6)	0.20 ± 0.45; 0.00 (0.00 to 0.00)	0.18 ± 0.46; 0.00 (0.00 to 0.00)	.959
Zarit caregiver burden (Δ12–6)	−8.00 ± 11.31; −4.00 (−20.00 to 0.00)	−1.74 ± 4.77; 0.00 (0.00 to 0.00)	.116

Note: Values are presented as mean ± standard deviation; median (25^{th}–75^{th} percentile). Δ12–6 indicates change calculated as 12-month minus 6-month values.

Discussion:

Our CRIM-Fos study represents the first real-world, multicenter, open-label, comparative observational research evaluating the tolerability and efficacy of

subcutaneous infusion of Foslevodopa/Foscarbidopa (FL/FC) with a comparative focus on White Caucasian and non-White PD patient cohorts"

The following key results were derived from our data.
A: Continuous subcutaneous FL/FC infusion was associated with sustained clinical benefits related to motor and sleep dysfunction in a multiracial cohort of patients with APD who are able to maintain and tolerate treatment for more than 12 months.

B: Motor function, motor complications, sleep quality, pain, caregiver burden, and health-related quality of life all showed meaningful improvement over time, with no worsening of excessive daytime sleepiness; the majority of gains emerged within the first six months and remained stable thereafter.

C: A time × race interaction analysis revealed statistically significant differences in motor improvement trajectories between the racial groups, highlighting the importance of cross-racial studies. While within-group Bonferroni-adjusted comparisons demonstrated significant improvements across all time contrasts in both groups ($p < .001$), the magnitude of improvement was greater among Caucasian patients. However, non-primary endpoints and interaction analyses should be considered exploratory and hypothesis-generating. Effect sizes are reported alongside p values to aid interpretation beyond statistical significance.

D: Within-race comparisons demonstrated continued reductions in caregiver burden from baseline to 12 months in the whole population and from 6 to 12 months among non-Caucasian patients (mean difference = 6.63, $p < .001$); the caregiver burden plateaued between 6 and 12 months among Caucasian patients. To our knowledge, the above observations, especially those related to racial differences, have not been reported before and merit discussion.

Using established tolerability criteria, our study confirms for the first time that FL/FC is effective, with high tolerability, across white and non-white PD patients as a long-term therapeutic option for advanced disease, and the results support the potential of FL/FC to address both patient-centred and caregiver-relevant outcomes beyond motor symptom control. Importantly, while overall trajectories indicated broad benefits, patterns of change over time differed by race for selected outcomes, suggesting heterogeneity in treatment responses. Dystonic pain and severe dyskinesias in treatment discontinuers occurred during the titration phase of FL/FC infusion and were considered dose-limiting adverse effects. Worsening

symptoms with dose escalation led to treatment cessation, primarily because of tolerability issues rather than a lack of efficacy.

Racial differences in treatment responses are well established in several long-term chronic conditions such as stroke, pain, and arthritis. Recently, the American Thoracic Society proposed a multilevel framework to engage minority populations in clinical research across pulmonary, critical care and sleep medicine areas [48]. The inclusion of currently underrepresented groups, such as non-white PD patients, in clinical trials is also important for determining potential differences in disease outcomes, responses to interventions, and therapeutic benefits, which can vary across different ethnic groups[49]. [50]

Differences in the evolution of non-motor symptoms, pain, hospital admissions, and caregiver burden highlight that clinical benefits are not uniform across populations, even within a standardized infusion framework. These findings underscore the importance of considering patient-level and population-level factors when evaluating longitudinal responses to advanced device-aided therapies and suggest that race may act as a proxy for broader biological, social, or health care-related determinants influencing treatment experience and disease burden. Our data show that from a tolerability and implementation perspective, the majority of patients were able to complete one year of therapy. We believe that the high rate of tolerability in white and non-white PD patients suggests that careful patient selection, close monitoring during dose escalation, and the proactive management of infusion-related and neuropsychiatric adverse effects are critical to maximizing long-term treatment persistence. Taken together, these findings address the study aims by demonstrating sustained effectiveness, identifying clinically relevant subgroup differences in longitudinal trajectories, and characterizing the real-world tolerability of FL/FC infusion.

While only 5 patients transitioned from the 24-hour infusion to the 12-hour infusion, the results indicate that the changes observed between 6 and 12 months were somewhat comparable in terms of motor efficacy but not non-motor outcomes. This issue would be better addressed in a dedicated, prospective study with predefined treatment strategies and an adequate sample size.

Our data confirm the motor efficacy of FL/FC, with UPDRS III scores improving from 40.26 ± 10.21 to 24.84 ± 6.67 over 12 months, indicating sustained treatment benefits. However, the UPDRS IV scores did not significantly change, suggesting that the effects of FL/FC on dyskinesias are less predictable than the effects of FL/FC on motor function. Additionally, the time × race interaction for the UPDRS IV score was not statistically significant, indicating similar dyskinesia trajectories across racial groups. We also found that body weight affected treatment response: a higher body mass index was correlated with lower UPDRS IV scores, whereas a lower body weight was correlated with a greater risk of dyskinesias.

A key and novel aspect of our study is the use of time × race interaction analysis and the reporting of racial differences in FL/FC responses. The rationale for this approach is supported by studies that have shown that the levodopa response in PD patients may be modified by racial diversity, which in turn may be mediated by genetic (such as catechol-o-methyl transferase polymorphisms or VPS13C heterozygous loss of function) or phenotypic issues (such as body weight).[44-46] Using the aforementioned analysis, we revealed statistically significant differences in motor improvement trajectories between the racial groups, highlighting the importance of cross-racial studies. While within-group Bonferroni-adjusted comparisons demonstrated significant improvements across all time contrasts in both groups ($p < .001$), the magnitude of improvement was greater among Caucasian patients. The data indicate that during FL/FC infusion, mean UPDRS III scores decreased by 18.59 points among Caucasian patients and by 10.06 points among non-Caucasian patients from baseline to 12 months; additionally, improvements in UPDRS III scores from 6 to 12 months were also greater among Caucasian patients (3.48 vs. 2.00 points). These findings suggest that higher doses of FL/FC may be required for equivalent efficacy in motor function improvement in non-white patients of Asian/Middle Eastern origin, further confirming the observations of Chaudhuri et al.[(11)] regarding relative hypo responsiveness to levodopa in Asian and black PD patients[11].

Our study revealed that for patients treated with FL/FC, mean PDSS scores significantly improved over time, indicating enhanced sleep quality. Specifically, the baseline mean score was 67.21 (SD = 14.69), which increased to 86.63 (SD = 22.36) at six months and further to 87.33 (SD = 18.95) at twelve months.

Notably, this improvement was consistent across both racial groups, suggesting that the beneficial effects of FL/FC on sleep quality are independent of racial diversity. Excessive daytime somnolence (EDS) is a significant contributor to poor quality of life in patients with APD and is often a common side effect of various anti-Parkinsonian therapies. Our analysis, which employed Bonferroni-adjusted pairwise comparisons, demonstrated significant reductions in ESS scores from baseline to six months (mean difference = 1.39, p = .004) and from baseline to twelve months (mean difference = 1.64, p < .001). To the best of our knowledge, this is the first report indicating that the tolerability of FL/FC is associated with a reduction in or stabilization of excessive daytime somnolence.

The above effects, which underpin the high tolerability of FL/FC across the two racial groups studied in this report, resulted in a significant improvement in health-related quality of life, as measured using the PDQ-8, from baseline to 6 months (mean difference = 4.31, p < .001) and from baseline to 12 months (mean difference = 6.11, p < .001). In addition, we investigated caregiver burden and found significant reductions in caregiver burden from baseline to 6 months (mean difference = 18.77, $p < .001$), from baseline to 12 months (mean difference = 22.09, $p < .001$), and from 6 to 12 months (mean difference = 3.31, $p < .001$). Interestingly, within-race comparisons using the time × race interaction also demonstrated continued reductions in caregiver burden from 6 to 12 months among non-Caucasian patients (mean difference = 6.63, $p < .001$), whereas the caregiver burden plateaued between 6 and 12 months among Caucasian patients. These differences could be multifactorial and need to be investigated further through community-based studies; however, the reduction in caregiver burden from the initiation of FL/FC is impressive. These findings should be interpreted cautiously given the sample size and multiplicity of endpoints.

Conclusion:

The subcutaneous infusion of FL/FC, which was shown to have high tolerability, offers enduring benefits for both motor and non-motor symptoms (sleep and excessive daytime somnolence) in patients with advanced Parkinson's disease. There are racial differences in motor responses, and our preliminary data suggest that higher doses of FL/FC may have been required for the non-white PD group investigated in this study, supporting previous observations. Regardless of race, there are beneficial effects of FL/FC on sleep quality as well as quality of life. Our study highlights the importance of meticulous patient selection, vigilant

monitoring during dose adjustments, and proactive side effect management to improve long-term adherence to treatment.

Limitations:

Our study has limitations that should be acknowledged when interpreting the findings. First, the lack of a comparator group in the observational design prevents causal conclusions and limits the ability to assess the efficacy of FL/FC relative to other treatments for APD. While the longitudinal design allows insights into changes over time, factors that were not measured and regression to the mean may have affected the results. Second, the sample size was relatively small, particularly for subgroup analyses by race, which may have led to underpowered interaction effects. Our study was underpowered to analyze fluctuations or dyskinesias, as UPDRS IV data did not show statistical significance. Consequently, any differences observed in the longitudinal trajectories should be interpreted with caution. Race was categorized into a binary system for statistical purposes, but this may overlook the complex biological, cultural, and health care differences within groups. As a result, these findings should be seen as hypotheses-generating rather than as conclusive evidence of different treatment responses. The analyses focused on treatment completers, characterizing the findings as exploratory rather than confirmatory. Excluding patients who discontinued treatment during titration may have introduced survivorship bias, meaning the observed effects reflect only those who tolerated therapy. This is a matter of clarification and transparency, not a methodological flaw, and no additional statistical analysis is necessary.

Declaration of competing interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit authorship contribution statement:

VM and KPD, the joint first authors, conceptualized the project and write up, while the other authors contributed by providing insights, writing, reviewing, editing, and finalizing the review.

Data Availability Statement:

The datasets are available from the corresponding author (vinod.metta@nhs.net) upon reasonable request.

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