Opicapone in UK Clinical Practice: Effectiveness, Safety and Cost Analysis in Patients with Parkinson's Disease

Running title: Opicapone in UK Clinical Practice

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Abstract

Aim: This subanalysis of the OPTIPARK study aimed to confirm the effectiveness and safety of opicapone in patients with Parkinson's disease (PD) and motor fluctuations in clinical practice specifically in the UK and to assess the impact of opicapone on treatment costs. **Methods:** Patients received opicapone added to levodopa for 6 months. Clinical outcomes were assessed at 3 and 6 months and treatment costs at 6 months. **Results:** Most patients' general condition improved at 3 months, with further improvements reported at 6 months. Opicapone improved motor and non-motor symptoms at both timepoints, was generally well tolerated, and reduced total treatment costs by £3718.60. **Conclusion:** Opicapone added to levodopa resulted in clinical improvements and reduced treatment costs across UK clinical practice.

Trial registration: Registered in July 2016 at clinicaltrials.gov (NCT02847442), clinicaltrials.gov/ct2/show/study/NCT02847442.

Key words: levodopa, opicapone, Parkinson's disease, motor fluctuations, health economics, cost-saving

Introduction

Levodopa (also known as L-DOPA) is the most effective symptomatic treatment for Parkinson's disease (PD); however, its long-term use is often associated with wearing-off symptoms.[1-4] Following its oral administration, it is catabolized in the periphery by dopa decarboxylase (DDC) and catechol-O-methyltransferase (COMT), with only 1% of an oral dose penetrating the brain.[5, 6] Peripheral Inhibitors of DDC (DDCIs) and COMT (COMTIs) are commonly used as adjunct therapy in order to increase bioavailability and enhance its delivery to the brain, with the aim of ameliorating wearing-off symptoms.[5, 7]

Opicapone was developed to fulfil the need for a more potent, longer-acting COMTI, with a good safety profile.[5, 6, 8, 9] It has been shown to be well tolerated and efficacious in reducing OFF-time in two large randomized, placebo-controlled, multinational pivotal trials in patients with PD and end-of-dose motor fluctuations (BIPARK-I and II).[10, 11] On the basis of these pivotal trials, opicapone was approved in the European Union as adjunct therapy to preparations of levodopa/DDCIs in adult patients with PD and end-of-dose motor fluctuations.[12] It has now also been approved in the USA, Japan, South Korea, Australia and other countries, with slight variations in its approved indications in each country.[13, 14]

Many regulators and payers encourage the supplementation of randomized trial data with real-world study evidence.[15, 16] OPTIPARK was a prospective, open-label, single-arm trial conducted in the UK and Germany,[17] with the primary intention to evaluate the change in the clinicians' perception of their patients' overall PD condition (as assessed by Clinician's Global Impression of Change [CGI-C]) after 3 months of treatment in routine clinical practice with once-daily opicapone 50 mg.[17] While patients in Germany were treated for 3 months only, patients in the UK were treated for 6 months to assess health economic costs. This subanalysis of OPTIPARK reports on the effectiveness and safety of opicapone after 3 and 6 months of treatment in the UK patients only and investigates the influence of opicapone on

overall treatment costs for patients with PD in real-world settings across the UK.

Materials and Methods

Study design

The study design of OPTIPARK has been described previously and the methods description partly reproduces their wording.[17] In brief, a prospective open-label, single-arm, multicenter trial evaluating opicapone 50 mg effectiveness in levodopa-treated patients with PD who experience motor fluctuations was conducted from November 2016 to July 2018 at 68 specialist neurology centers across the UK and Germany (EudraCT Number: 2016-002391-27).[17] This subanalysis focuses on the outcomes from the patients in the UK centers only.

Patients received opicapone 50 mg capsules once daily at bedtime, at least one hour before or after the last daily dose of levodopa/DDCI. Whereas patients in the German cohort were treated for 3 months, patients in the UK were treated for 6 months to investigate the influence of opicapone treatment on the health economic costs caused by PD. At the end of the study, patients could continue opicapone in line with local standard practice.

Study population

Patients with idiopathic PD aged ≥30 years were eligible if they reported symptoms of motor fluctuations as identified by at least one symptom on the 9-Symptom Wearing-off Questionnaire (WOQ-9).[18] They also had to be Hoehn and Yahr stages I–IV (during ON-time) and treated with 3–7 daily doses of levodopa/DDCI. Patients with symptoms and signs suggestive of atypical parkinsonism, severe unpredictable OFF periods (investigator judgment) and severe hepatic impairment (Child-Pugh Class C) were excluded. The full list of inclusion and exclusion criteria has been detailed previously.[17]

Study assessments

Endpoints were assessed at baseline, and at 1, 3 and 6 months or at any early discontinuation visit. The primary outcome was CGI-C (7-point scale, ranging from very

much improved to very much worse), which assessed the clinicians' perception about their patients' illness after 3 months treatment with opicapone 50 mg; the same rater assessed CGI-C throughout the study and before the patient made his/her own assessment. Secondary assessments included CGI-C after 6 months of treatment and Patient's Global Impression of Change (PGI-C), WOQ-9 assessments, the Unified Parkinson's Disease Rating Scale (UPDRS) sections I–IV,[19] the Parkinson's Disease Questionnaire (PDQ-8),[20] the Non-motor Symptoms Scale (NMSS),[21] and change from baseline in total daily levodopa dose and dosing frequency after 3 and 6 months.

Health economic costs were evaluated using the Client Service Receipt Inventory (CSRI) questionnaire, which was adapted to assess the effect of 6 months opicapone treatment on costs for the care of patients with PD in the UK. The questionnaire was grouped into four sections. Section 1 contained the categories 'hospital and residential services' and 'primary and community care services'. Section 2 contained 'investigations/diagnostic tests', 'aids or devices' and 'adaptations to the home'. Section 3 contained 'informal care', 'care because of multiple system atrophy (MSA)' and 'journeys'. Section 4 contained 'occupation' and included questions regarding full- and part-time gross wage, stopped or reduced working and unemployed/retired time. Categories from sections 1 and 2 were considered 'formal service' whereas categories from sections 3 and 4 were considered 'unpaid care' for the purposes of the cost evaluation. The questionnaire was completed by the investigator at baseline and after 6 months of treatment. All economic calculations were made in pounds sterling.

Treatment compliance was calculated based on the numbers of dispensed and returned opicapone capsules, and treatment duration excluding interruptions to study medication. Safety was assessed through the specific reporting of treatment emergent adverse events (TEAEs) as well as vital signs and physical and regular neurological examinations. Pre-

specified sub-group analyses also evaluated change from baseline in levodopa total daily dose in patients who reported dopaminergic adverse events (AEs; i.e. dyskinesia, nausea, vomiting, orthostatic hypotension, any hallucination, illusion, delusion or disturbance in attention).

Statistical analysis

No sample size estimation was performed for this open-label study. The safety population included all patients who received ≥1 dose of opicapone. Effectiveness was assessed in the full analysis set (FAS) which included all patients in the safety population who had ≥1 CGI-C recorded post-baseline. The Per-protocol set (PPS) included all patients of the FAS without any major protocol deviation. Analyses were descriptive; any missing values for the primary outcome measure (CGI-C) at 3 months were imputed using the last observation carried forward method. For UPDRS II (at ON and OFF), UPDRS III (at ON), UPDRS II plus III (at ON), PDQ-8 and NMSS the means of changes from baseline were analyzed using Student's t-test.

The formal service costs and unpaid care costs within the economic evaluation were determined using generalized linear models with a gamma distribution and log-link function at baseline and at month 6. The dependent variables of the model were the total formal service costs or total unpaid care service costs; explanatory variables of the model were age, gender, duration of PD, duration of wearing-off motor fluctuations, UPDRS part I, UPDRS part II (ADL) score at OFF stage, UPDRS II (ADL) plus III (motor function) during the ON stage, UPDRS part IV, total unpaid care service cost (if dependent variable was total formal service cost) and total formal service cost (if dependent variable was total unpaid care service cost). In order to compare two regression models at baseline and at month 6, a sensitivity analysis was performed. Regression analyses at baseline and at month 6 were performed only for patients with all model data available at both visits. Significance level in order to decide whether there is a significant relationship between the variables in the regression model of the data set was 0.05.

Data from 13 enrolled patients (including 11 treated patients) at one UK site were incomplete

and inconsistent and were therefore excluded from the final analysis before the database was locked.

Results

Patient disposition and baseline characteristics

This subanalysis includes 147 patients enrolled at 19 centers across the UK, 143 (97.3%) of whom received ≥1 dose of opicapone (**Figure 1A**). The final safety set comprised 132 patients, excluding the 11 patients treated at the excluded site (**Figure 1B**). Of these, 128 (97.0%) patients had ≥1 post-baseline CGI-C assessment and were included in the FAS. In the final safety set, there were 37 patients (28.0%) who terminated the trial prematurely and stopped treatment with opicapone. A total of 30 patients (22.7%) withdrew due to a TEAE, including 26 patients (19.7%) who withdrew due to a possibly related TEAE and 1 patient (0.8%) due to lack of efficacy. Treatment compliance was high, with a mean ± SD treatment compliance rate of 98.1 ± 7.88%. The majority of patients complied with ≥80% of doses. Most of the patients who completed the trial continued to receive opicapone on prescription (84/95; 88.4%).

Baseline characteristics of the safety analysis set are shown in **Table 1**. The study population comprised more men (>60%) than women, with a mean age of 67.3 ± 8.4 years. The mean time since diagnosis was 8.93 ± 5.15 years and the mean duration of motor fluctuations was 2.62 ± 2.8 years. At study entry, the majority of patients (73.5%) received concomitant PD treatment, including rasagiline (30.3%), pramipexole (23.5%) and ropinirole (23.5%).

Clinician and Patient Global Impressions of Change

After 3 months of opicapone, clinical improvement on the CGI-C scale was observed for 72.6% of patients, including 48% who were judged by the investigator as ‘much improved’ or

'very much improved' (**Figure 2A**). Patient self-rated levels (PGI-C) also improved, with the majority of patients (78.4%) reporting an improvement after 3 months of treatment, including 52% who reported as 'much improved' or 'very much improved' (**Figure 2B**). After 6 months of treatment, the proportion of patients with clinical improvement further increased as judged by the investigators (CGI-C of 85.3%; **Figure 2C**) and the patients (PGI-C of 79.8%; **Figure 2D**), with 58% and 53% reported as 'much improved' or 'very much improved' for CGI-C and PGI-C, respectively.

Wearing-off symptoms

The number of patients experiencing individual wearing-off symptoms, as assessed using the WOQ-9, was lower after 3-months treatment with opicapone compared with baseline. After 6 months, a further decrease was reported for all symptoms except cloudy mind and slowness of movement which showed no further reduction between 3 and 6 months (**Figure 3)**.

Rating scale outcomes

UPDRS I scores demonstrated no change in mentation, behavior and mood after 3 months (0.0 ± 1.7 points) and a slight increase from baseline after 6 months of treatment (0.2 ± 1.8 points; **Table 2**). Improvements in activities of daily living (ADL, UPDRS II) during OFF time, motor function (UPDRS III) during ON time and total scores (UPDRS II + III) during ON time were observed at both 3 and 6 months. After 3 months, UPDRS II and III scores decreased by 2.2 ± 4.9 points and 2.7 ± 8.3 points, respectively, with further reductions observed after 6 months of treatment (UPDRS II: 2.4 ± 5.8 points, p=0.0002; UPDRS III: 3.3 ± 10.1 points, p=0.0002). Combined UPDRS II and III scores during ON time decreased by 3.7 ± 10.7 after 3 months and remained low after 6 months (3.4 ± 22.2 points, p=0.0007). UPDRS II scores during ON time decreased by 0.5 ± 4.49 points and by 0.1 ± 4.6 points after 3 and 6 months,

respectively. UPDRS IV scores (complications of therapy in the past week) were reduced by 0.6 ± 2.3 points after 3 months and by 0.1 ± 2.5 after 6 months of treatment. PDQ-8 and NMSS assessments demonstrated improvements in quality of life and non-motor symptoms, respectively, with a decrease of -4.4 ± 13.6 points for PDQ-8 and -4.1 ± 22.7 points for NMSS after 3 months, and -2.4 ± 15.2 points for PDQ-8 and -1.5 ± 25.8 points for NMSS after 6 months of opicapone treatment.

Client Service Receipt Inventory questionnaire

Total service costs during the 6 months prior to study participation were £183,476.70, mainly driven by primary and community care (66.75%) and hospital and residential (22.96%) services costs (**Table 3**). Average total costs were 13,537.62, including £2334.97 for formal service and £12806.51 for unpaid care costs. After 6 months of opicapone treatment, total service costs, including costs for hospital and residential services, primary and community care services, investigations/diagnostic tests, aids or devices and adaptations to the home, had reduced to £121,280.83, mainly driven by hospital and residential (46.75%) and primary and community care (36.30%) services costs. The cost reduction at 6 months is further confirmed by the decrease in the cost of care per individual patient throughout the different domains, apart from the costs for investigations or diagnostic tests, which increased slightly after 6 months of opicapone treatment (**Table 3**). Mean total costs decreased at Month 6 by £3718.60, including a reduction of £987.41 for formal service and £2920.96 for unpaid care costs.

A regression analysis demonstrated a statistically significant relationship for formal service costs and UPDRS part I (estimate ± standard error [SE]=0.134 ± 0.064; 95% confidence interval [CI] 0.008–0.259; p=0.036) and part IV scores (estimate ± SE=0.098 ± 0.040; 95% CI 0.020–0.177; p=0.014) at baseline (FAS). A similar analysis in the PPS confirmed the significance for UPDRS part IV (estimate ± SE=0.100 ± 0.034; 95% CI 0.016–0.183; p=0.02) but not UPDRS part I scores at baseline. In addition, the sensitivity analysis (FAS)

performed only for patients with all model data available at both visits supported the significant relationship for formal service costs and UPDRS part I at baseline (estimate ± SE=0.206 ± 0.083; 95% CI 0.044–0.368; *p*=0.013). No significant relationship for formal service costs was observed for any of the explanatory variables at 6 months.

Statistically significant relationships for unpaid care costs were observed for the duration of wearing-off motor fluctuations (estimate ± SE=-0.017 ± 0.005; 95% CI -0.027–-0.006; *p*=0.002), UPDRS part I (estimate ± SE=0.207 ± 0.101; 95% CI 0.010–0.404; *p*=0.040), UPDRS part II at OFF stage (estimate ± SE=0.099 ± 0.040; 95% CI 0.020–0.177; *p*=0.014), and part IV scores (estimate ± SE=0.228 ± 0.078; 95% CI 0.074–0.381; *p*=0.004) at baseline and for females (estimate ± SE=1.527 ± 0.595; 95% CI 0.362–2.693; *p*=0.010), and UPDRS part I (estimate ± SE=0.325 ± 0.116; 95% CI 0.098–0.552, *p*=0.005) at month 6 (FAS). The PPS supported these results with the exception of the UPDRS part I scores at baseline, which demonstrated a non-significant relationship. At month 6, the regression analysis in the PPS showed significant relationships for the same variables as in the FAS and in addition, for UPDRS part II at OFF stage. The sensitivity analysis (FAS) also supported the results; only for UPDRS part I and part IV scores at baseline no statistically significant differences were observed.

Levodopa dosing

Treatment with opicapone for 3 months appeared to have little effect on the total daily levodopa dose and the number of daily doses. The majority of patients (72.5%) reported no change in the total daily dose, 16.7% had a dose increase and 10.8% a dose decrease. With regard to levodopa dosing frequency, 69.6% of patients reported no change, 11.8% had an increase and 18.6% had a decrease in dosing frequency. At 3 months, the overall mean ± SD change in total daily dose from baseline was approximately -26.2 ± 130.04 mg levodopa per day. Similar observations were made after 6 months of treatment, with the majority of

patients (71.6%) remaining on the same total daily levodopa dose, 16.8% of patients reporting a dose increase and 11.6% a dose decrease. A total of 67.4% of patients reported no change in levodopa dosing frequency, 14.7% showed an increase and 17.9% a decrease. At 6 months, the overall mean ± SD change of total daily dose from baseline was approximately -25.5 ± 133.24 mg levodopa per day.

For patients who reported dopaminergic AEs (FAS), most patients (55.8%) remained on the same total daily levodopa dose, 16.3% had a dose increase and 27.9% a dose decrease, resulting in an overall mean ± SD change of -30.8 ± 158.85 mg/day. After 6 months of treatment, an overall mean ± SD change of -28.1 ± 167.87 mg/day was reported in patients with dopaminergic AEs. For patients who experienced dyskinesia (FAS) and ended the 6 months of treatment, most patients (47%) had a dose decrease, resulting in an overall mean ± SD change of -183.9 ± 135.7 mg/day. Overall, 27 (28%) out of 95 patients had a levodopa reduction and ended the 6 months of treatment with an overall mean ± SD change of approximately -178.7 mg ± 129.1 mg levodopa per day. Out of these 27 patients, 14 (52%) reported dyskinesia and 10 (71%) were resolved by the end of the 6 months of treatment.

Safety and tolerability

TEAEs occurred in 119 (90.2%) patients and were mostly mild or moderate (**Table 4**). TEAEs that were considered as at least possibly related to treatment were observed in 86 (65.2%) patients, with dyskinesia (27.3%) and dry mouth (12.1%) being the most frequent of these (≥3%), in line with previous reports. No patient experienced explosive diarrhea after 6 weeks of treatment, which is a common side effect associated with other COMTIs. Most side effects were reported during the first week of treatment and the incidence was very low from the third to fourth week onwards (**Figure 4**). At least possibly-related serious TEAEs were uncommon, with a reported frequency of 1.5%. A total of 30 (22.7%) patients terminated prematurely due to TEAEs, the two most common being dyskinesia in 5 (3.8%) patients and

abnormal dreams in 4 patients (3.0%). Two out of the 5 patients that discontinued due to dyskinesia had a levodopa dose reduction during the study. No patient demonstrated any relevant changes in vital signs, physical and neurological examinations throughout the study.

Discussion

This OPTIPARK subanalysis confirmed the effectiveness, safety and tolerability of opicapone in UK clinical practice, with a demonstrable cost-saving impact. Similar to what has been reported for the overall study population,[17] most patients' global PD condition was improved with opicapone (≥72.5% as judged by clinicians and the patients themselves) 3 months after they started treatment. In the UK cohort, further clinical improvements were reported after 6 months of treatment. Opicapone was generally well tolerated, with observed AEs in line with those reported in the overall OPTIPARK population and those reported for other dopaminergic treatments.

PDQ-8 assessments demonstrated that opicapone was also associated with an improvement in overall quality of life at both 3 and 6 months of treatment. UPDRS ADL scores (UPDRS II) during OFF time and motor scores (UPDRS III) during ON time also improved after 3 months and continued to improve after 6 months of opicapone treatment. UPDRS scores for mentation, behavior and mood (UPDRS I) remained low after 3 months and slightly increased after 6 months of treatment compared with baseline. Given the already very low scores at baseline, the likelihood of observing any improvement in these scores is relatively low compared with that of observing no change or worsening of effect. As shown for the overall population,[17] treatment with opicapone was not only associated with a reduction in OFF time and an increase in ON time, but also an improvement in the quality of ON time in patients in the UK. Non-motor symptoms are another important source of disability and contributor to a worse quality of life for people living with PD.[22, 23] The pivotal BIPARK-I and II studies as well as the overall OPTIPARK study suggested an overall

improvement in non-motor symptoms,[10, 11, 17] which was further confirmed in this OPTIPARK subanalysis.

Opicapone 50 mg was generally well tolerated in patients with PD in routine clinical practice in the UK, with the most frequently reported TEAEs in keeping with the known safety profile of opicapone.[10, 11, 13, 17] The majority of AEs were mild to moderate in severity and occurred primarily during the first week of treatment. A large proportion of patients (22.7%) withdrew from the study due to AEs but causative types of AEs were diverse. The most frequent AE leading to study discontinuation was dyskinesia affecting only 5 patients (3.8%). Diarrhea has been considered a common side effect of COMT inhibitors,[24] but there were no TEAEs or SAEs related to this event in this UK cohort and there is accumulating data to suggest that this is a rare complication with opicapone.[25, 26] Orange urine discoloration, which is frequently reported with entacapone use, was also not observed with opicapone treatment.

This OPTIPARK subanalysis also assessed the impact of opicapone on overall treatment costs in patients with PD treated in routine clinical practice in the UK. As PD advances, medical needs increase, resulting in higher costs in the later stages of the illness. A recently completed study on the economic cost of PD in the UK has shown a financial burden amounting to over £16,500 per patient household per year. The annual cost of treatment to the National Health Service was estimated at £2,118 per patient and the total annual economic burden at £20,123 per household.[27] Other studies have estimated that PD is the third-most costly physically debilitating neurological disease after multiple sclerosis and stroke, on a cost per case basis.[28] The recurring financial expenses and reduced income of the patient and their carers can directly impact the living/health conditions and quality of life of those involved, who often find themselves in financial distress.[29] Several studies have shown that costs increase as PD advances,[30, 31] and one UK-based study indicated

that some of this increased cost is related to time spent in the OFF state.[30] Average 12-monthly total costs increased according to the time spent in the OFF state from £25,630 in patients spending less than 25% of their waking hours in OFF to £62,147 for patients spending more than 75% of their time in OFF. New treatment strategies that can alleviate the impact of the disease without adding considerably to the already high-cost burden of the disease are to be welcomed.

In this analysis of the UK cohort, an apparent cost-saving was observed after 6 months of treatment, with a mean total service cost decrease of £3718.60. This constituted a saving of approximately £987 on formal service costs and, importantly, a £2,920 saving on unpaid care costs. Unpaid care costs included work loss-related costs and informal care, which would primarily affect the household cost to the patient and their carer. These findings point towards the potential for opicapone to reduce the financial burden of PD to patients and their carers, as well as to healthcare and social care services. In an analogous situation, addition of opicapone to levodopa infusion therapy in advanced PD has also shown cost-savings.[32] Additional studies will be required to explore this possibility over the longer term and across different settings.

Limitations of the study include those inherent to open-label studies without placebo control, where both the clinician and patient have expectations from treatment, and are therefore at risk of placebo effects and investigator bias. As the population by definition included patients struggling in the period before recruitment, there is a possibility that some of the change may simply reflect regression to the mean. Whether formal protocol of levodopa dose adjustment may have further improved tolerability requires further study. However, despite these limitations, these real-world data complement the evidence from clinical trials, confirming that opicapone is generally well tolerated, with positive impact on quality of life, and potential important net cost savings.

Conclusions

Once-daily opicapone 50 mg added to levodopa therapy in patients with PD and motor fluctuations was effective and generally well tolerated in routine clinical practice across the UK. The patients' overall PD condition as judged by the clinicians and the patients was clinically improved after 3 and 6 months of treatment. Opicapone was associated with an improvement of both motor and non-motor symptoms and quality of life after 3 and 6 months of treatment, and had a cost-saving impact that could benefit patients, their carers as well as healthcare and social care systems.

Summary points

- Opicapone is a catechol-O-methyltransferase (COMT) inhibitor that proved effective in treating wearing-off symptoms when given as adjunct to levodopa therapy in patients with Parkinson's disease (PD) and motor fluctuations in two large randomized, placebo-controlled trials (BIPARK-I and II).
- The OPTIPARK study, a prospective, open-label, single-arm study conducted in clinical practices across the UK and Germany, confirmed the effectiveness and safety of 3-month treatment with opicapone in real-world settings.
- While patients in Germany were treated for 3 months only, patients in the UK were treated for 6 months to assess health economic costs.
- This OPTIPARK subanalysis reports the clinical outcomes after 3 and 6 months of opicapone treatment in the UK patients only and the impact of opicapone on overall treatment costs for patients with PD in clinical practice in the UK.
- In the UK cohort, patients' overall PD condition as judged by the clinicians and the patients was clinically improved after 3 months, with further improvements observed after 6 months of treatment.
- Opicapone was associated with an improvement of both motor and non-motor symptoms and quality of life after 3 and 6 months of treatment.
- In line with the overall OPTIPARK population, treatment with opicapone was generally well tolerated, with the majority of the adverse events reported being of mild or moderate severity.
- Opicapone had an apparent cost-saving impact after 6 months of treatment in patients with PD in the UK; with a mean reduction in total service costs by £3718.60.

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Authors contributions

CS, RC, CC, JS, NP, JE, TF, and AL were study investigators in the UK, were involved in the study design, data collection, and data interpretation and contributed equally to the first draft. PSS participated in the study design, data collection, data management, and data analysis. All authors provided critical review of the manuscript, and read and approved the final draft.

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Ethical conduct of research

Institutional review boards at the participating sites approved the protocol and the trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided written informed consent.

Data sharing statement

The dataset supporting the conclusions of this article is included within the article. The study sponsor (BIAL) undertakes to share, upon request, anonymized patient-level, study-level clinical trial data (analyzable data sets), and other information (such as protocols) from this clinical trial to qualified researchers as necessary for conducting legitimate research. Information is provided at www.bial.com.

Figure legends

Figure 1. Patient disposition for [**A**] study population enrolled and [**B**] safety set (excluding one trial site). AE, adverse event

Figure 2. Global Impression of Change following treatment with opicapone 50 mg [**A**] investigator-rated after 3 months/LOCF (CGI-C, primary endpoint, n=128); [**B**] self-rated by the patient after 3 months (PGI-C, n=102); [**C**] investigator-rated after 6 months (CGI-C, n=95); [**D**] self-rated by the patient after 6 months (PGI-C, n=94). CGI-C, Clinicians' Global Impression of Change; LOCF, Last Observation Carried Forward; PGI-C, Patients' Global Impression of Change

Figure 3. Presence of wearing-off symptoms as assessed on the WOQ-9 at baseline and after 3 and 6 months of treatment. WOQ-9, 9-Symptom Wearing-off Questionnaire

Figure 4. Frequency of distribution of at least possibly related TEAEs to opicapone treatment. TEAE, treatment emergent adverse event