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Opicapone Use in Clinical Practice across Germany: A Sub-Analysis of the OPTIPARK Study in Parkinson's Disease Patients with Motor Fluctuations

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Keywords
Levodopa · Motor fluctuations · Opicapone · Parkinson's disease · Real-world study

Abstract
Introduction: The OPTIPARK study confirmed the effectiveness and safety of opicapone as adjunct therapy to levodopa in patients with Parkinson's disease (PD) and motor fluctuations under real-world conditions. The aim of this sub-analysis was to evaluate opicapone in the German patient cohort of OPTIPARK in order to provide country-specific data. ***Methods:*** OPTIPARK was an open-label, single-arm study conducted in routine clinical practice across Germany and the UK. Patients with PD and motor fluctuations received once-daily opicapone 50 mg for 3 months in addition to levodopa. The primary endpoint was Clinicians' Global Impression of Change (CGI-C). Secondary assessments included Patients' Global Impressions of Change (PGI-C), Unified Parkinson's Disease Rating Scale (UPDRS) I–IV, Parkinson's Disease Questionnaire (PDQ-8), and Non-Motor Symptoms Scale (NMSS). This sub-analysis reports outcomes from the German patients only. ***Results:*** Overall, 363 (97.6%) of the 372 patients included in the German cohort received ≥1 dose of opicapone and 291 (80.2%) completed the study. Improvements on CGI-C and PGI-C were reported by 70.8% and 76.3% of patients, respectively. UPDRS scores improved for activities of daily living during OFF time by −3.3 ± 4.5 points and motor scores during ON time by −5.3 ± 7.9 points. PDQ-8 and NMSS scores also demonstrated improvements. Treatment emergent adverse events considered at least possibly related to opicapone occurred in 37.7% of patients, with most being of mild or moderate intensity. ***Conclusion:*** Opicapone added to levodopa in patients with PD and motor fluctuations was effective and generally well tolerated in routine clinical practice across Germany.

Introduction

Levodopa, also known as L-DOPA, is an effective and generally well-tolerated dopamine replacement agent that is widely used to treat Parkinson's disease (PD) [1–3].

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However, long-term use of levodopa can cause wearing-off symptoms, other motor and non-motor fluctuations and dyskinesias, which can affect mobility, activities of daily living, and communication [4, 5]. Wearing-off symptoms are experienced by 40–50% of patients treated for 5 years and affect approximately two-thirds of patients after 10 or more years of levodopa therapy [6]. To manage these symptoms, catechol-O-methyltransferase (COMT) inhibitors are commonly used as an adjunct to levodopa [7, 8]. The inhibition of dopa decarboxylase (DDC) and COMT, two enzymes involved in metabolizing levodopa, increases levodopa bioavailability and its delivery to the brain, thereby ameliorating wearing-off symptoms [9–12].

Opicapone is a once-daily COMT inhibitor developed for increased potency and longer-acting COMT inhibition [7, 9, 13–15]. Two large randomized trials (BIPARK-I and -II) demonstrated that opicapone is generally well tolerated and efficacious in reducing OFF-time in patients with PD and end-of-dose motor fluctuations [15, 16], which led to the drug's approval in Europe as adjunctive therapy to preparations of levodopa/DDC inhibitors [17].

While randomized-controlled trials are essential for assessing the efficacy and safety of new treatments, they are usually conducted in highly selective patient populations under restricted conditions that do not mimic real-life situations [18–20]. Evidence from everyday clinical practice is encouraged to complement data from randomized controlled trials, and is now being used more frequently to support regulatory decision-making and pharmacovigilance studies [19, 21, 22]. OPTIPARK was a prospective, open-label, single-arm study on the use of opicapone in patients with PD and motor fluctuations across Germany and the UK under clinical practice conditions, with the primary aim of evaluating the change in the clinician's view of their patients' global PD condition after 3 months of treatment. OPTIPARK was the first study to confirm the effectiveness, safety and tolerability of once-daily opicapone 50 mg in routine clinical practice [23]. This report focuses on a sub-analysis of the German cohort only and will provide clinicians with data on the effectiveness and tolerability of opicapone 50 mg in routine clinical practice specifically in Germany.

Methods

Study Design

The study design has been described previously [23]. In brief, a prospective open-label, single-arm, multicenter trial investigating the effectiveness of opicapone 50 mg in levodopa-treated patients with PD who experience motor fluctuations was carried out

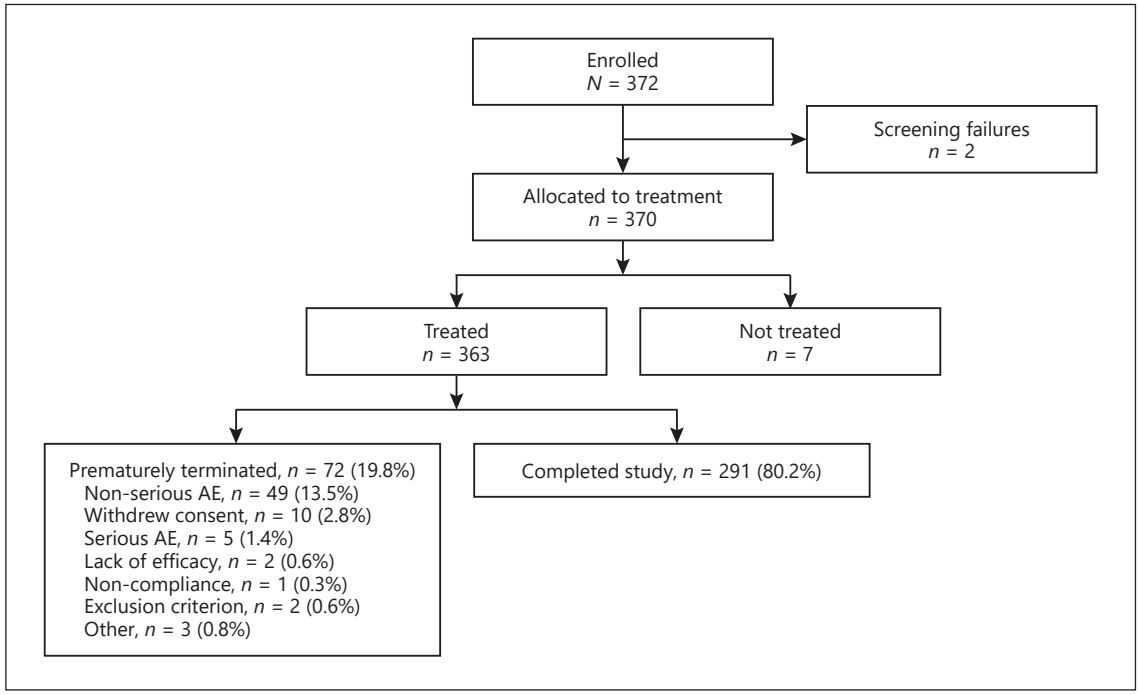

Fig. 1. Patient disposition.

between November 2016 and July 2018 at 68 specialist neurology centers across Germany and the UK (EudraCT number: 2016-002391-27). This sub-analysis will report the outcomes from the German patients only who were treated at 49 centers across Germany.

Patients received opicapone 50 mg capsules once-daily at bedtime, at least 1 h after the last daily dose of levodopa/DDC inhibitor. The total duration of treatment within the German cohort was 3 months.

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) [24]. They also had to be Hoehn and Yahr stages I–IV (during ON) and treated with 3–7 daily doses of levodopa/DDC inhibitor. Details of the inclusion and exclusion criteria have previously been reported [23].

Study Assessments

Endpoints were assessed at baseline, 1 month and 3 months or at any early discontinuation visit. The primary endpoint was the Clinicians' Global Impression of Change (CGI-C; 7-point scale, from very much improved to very much worse), which assessed the clinician's view of the patient's global PD condition after 3 months of treatment with opicapone 50 mg. Secondary assessments included the Patient's Global Impression of Change (PGI-C), WOQ-9 assessments, the Unified Parkinson's Disease Rating Scale (UPDRS) sections I–IV during ON and/or OFF time [25], the Parkinson's Disease Questionnaire (PDQ-8) [26], the Non-Motor Symptoms Scale (NMSS) [27] and change from baseline in total daily levodopa dose and dosing frequency. Safety was assessed through reporting of treatment emergent adverse events (TEAEs) as well as vital signs and routine physical and neurological examinations.

Statistical Analysis

No sample size estimation was performed. The safety population included all patients who received ≥1 dose of opicapone. Effectiveness was assessed in the full analysis set which included all patients in the safety population who had ≥1 CGI-C recorded post-baseline. Analyses were primarily descriptive; missing values for the primary outcome measure (CGI-C) at 3 months was imputed using the last observation carried forward method.

Table 1. Baseline characteristics (safety set)

Category	*N* = 363
Age, years; mean ± SD (range)	67.8±9.21 (45–87)
Age categories, *n* (%)	
≥30 to <65	125 (34.4)
≥65 to <85	233 (64.2)
≥85	5 (1.4)
Sex (M/F), *n* (%)	234 (64.5)/129 (35.5)
Race, *n* (%)	
White	363 (100.0)
Duration of Parkinson's disease, months	
Mean ± SD	100.3±58.74
Median (range)	89 (5–420)
Duration of motor fluctuations, months	
Mean ± SD	29.7±39.47
Median (range)	14.5 (0–324)
Symptoms (WOQ-9 assessment),* *n* (%)	
Tremor	215 (61.6)
Any slowness of movement	333 (95.4)
Mood changes	189 (54.2)
Any stiffness	287 (82.2)
Pain/aching	206 (59.0)
Reduced dexterity	317 (90.8)
Cloudy mind/slowness of thinking	154 (44.1)
Anxiety/panic attacks	71 (20.3)
Muscle cramping	204 (58.5)
Total levodopa daily dose, mg; mean ± SD	552.9±244.61
Median (range)	500.0 (100–1,500)
Adjunct therapies,#*n* (%)	
Rasagiline	96 (26.4)
Pramipexole	92 (25.3)
Amantadine	89 (24.5)
Ropinirole	80 (22.0)
Safinamide	64 (17.6)
Rotigotine	54 (14.9)
Piribedil	44 (12.1)

SD, standard deviation; WOQ-9, Wearing-off Questionnaire (9 items). * Assessed in the full analysis set. # Patients could take ≥1 adjunct therapy.

Results

Patient Disposition and Baseline Characteristics

Three-hundred and seventy-two patients were enrolled at 49 centers across Germany. Of these, 363 (97.6%) patients received at least one dose of opicapone (safety set) and 349 (93.8%) had at least one post-baseline CGI-C assessment and were included in the full analysis set (Fig. 1). A total of 72 (19.8%) patients prematurely terminated the trial and discontinued treatment with opicapone. While 54 patients (14.9%) withdrew due to a TEAE (including 11.0% [*n* = 40] due to an at least possibly related TEAE), two (0.6%) withdrew because of lack of efficacy. A high proportion of patients (92.6%) complied with ≥80% of doses. The mean ± standard deviation (SD) treatment compliance was 99.7 ± 8.19%. Of the 291 patients who completed the trial, 248 patients (71.1%) continued to receive opicapone by prescription.

Baseline characteristics of the safety set are provided in Table 1. The study population was comprised of white Caucasian patients with a mean ± SD age of 67.8 ± 9.2 years, a mean ± SD time since diagnosis of 100.3 ± 58.7 months and a mean ± SD duration of motor fluctuations

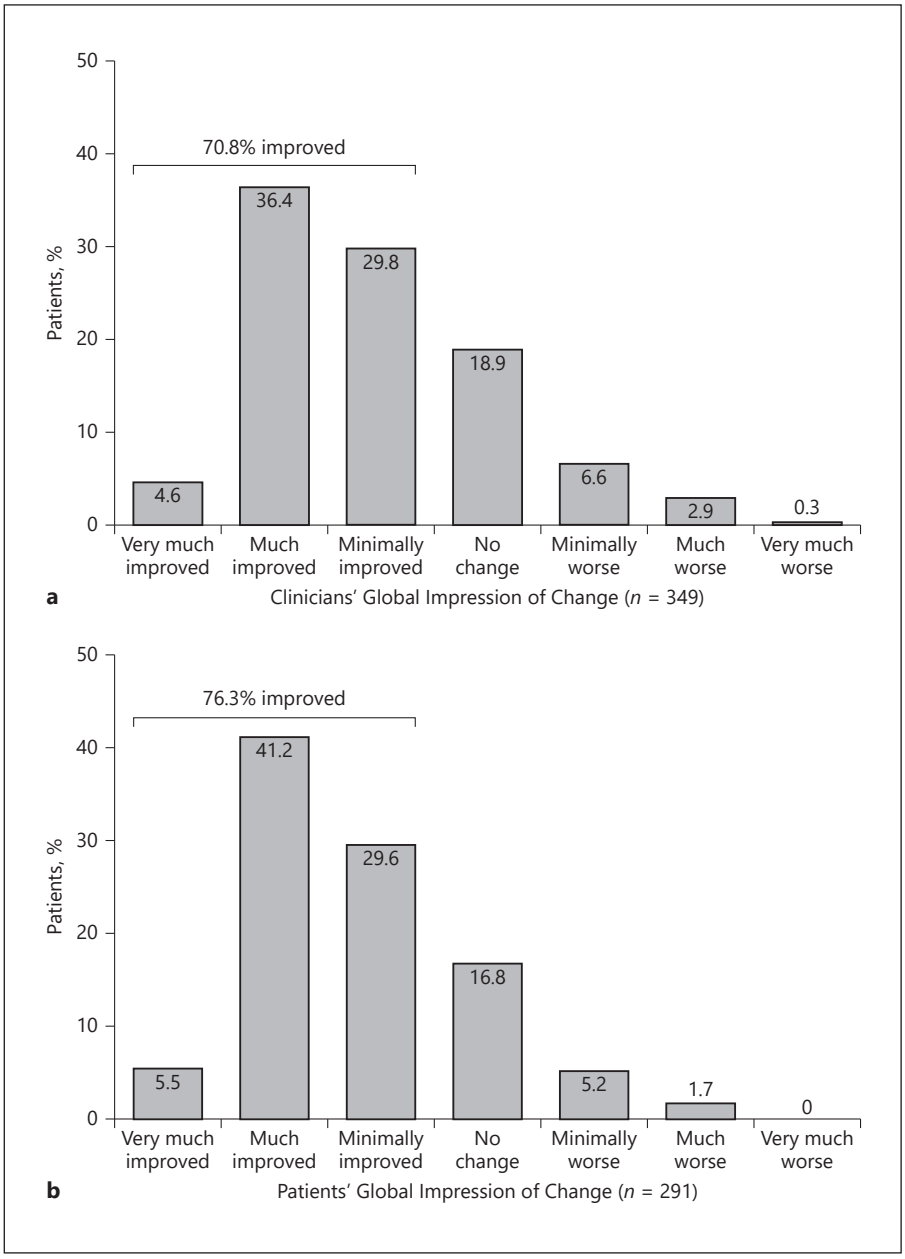

Fig. 2. Global impression of change following 3 months of treatment with opicapone 50 mg (LOCF) (**a**) investigator rated (CGI-C, n = 349); (**b**) self-rated by the patient (PGI-C, n = 291). CGI-C, Clinicians' Global Impression of Change; LOCF, Last Observation Carried Forward; PGI-C, Patients' Global Impression of Change.

of 29.7 ± 39.5 months. Total mean ± SD levodopa daily dose in the safety set was 552.9 ± 244.61. The majority of patients (80.7%) received another levodopa adjunct medication: the most common reported adjunct medications were rasagiline (26.4%), pramipexole (25.3%), and amantadine (24.5%).

Clinician and Patient Global Impressions of Change

The majority of patients (70.8%) demonstrated clinical improvements after 3 months of treatment with opicapone 50 mg, as judged by the investigators (CGI-C), with 41% reporting as much or very much improved (Fig. 2a). Patients' self-rated levels of improvement (PGI-C) were consistent with the PGI-C results of the primary OPTIPARK study, with the majority of patients (76.3%) reporting an improvement after 3 months of treatment with opicapone 50 mg (Fig. 2b). Similar results were already reported at the 1-month assessment, with 72.8% and 71.2% of patients reporting improvements on CGI-C and PGI-C, respectively.

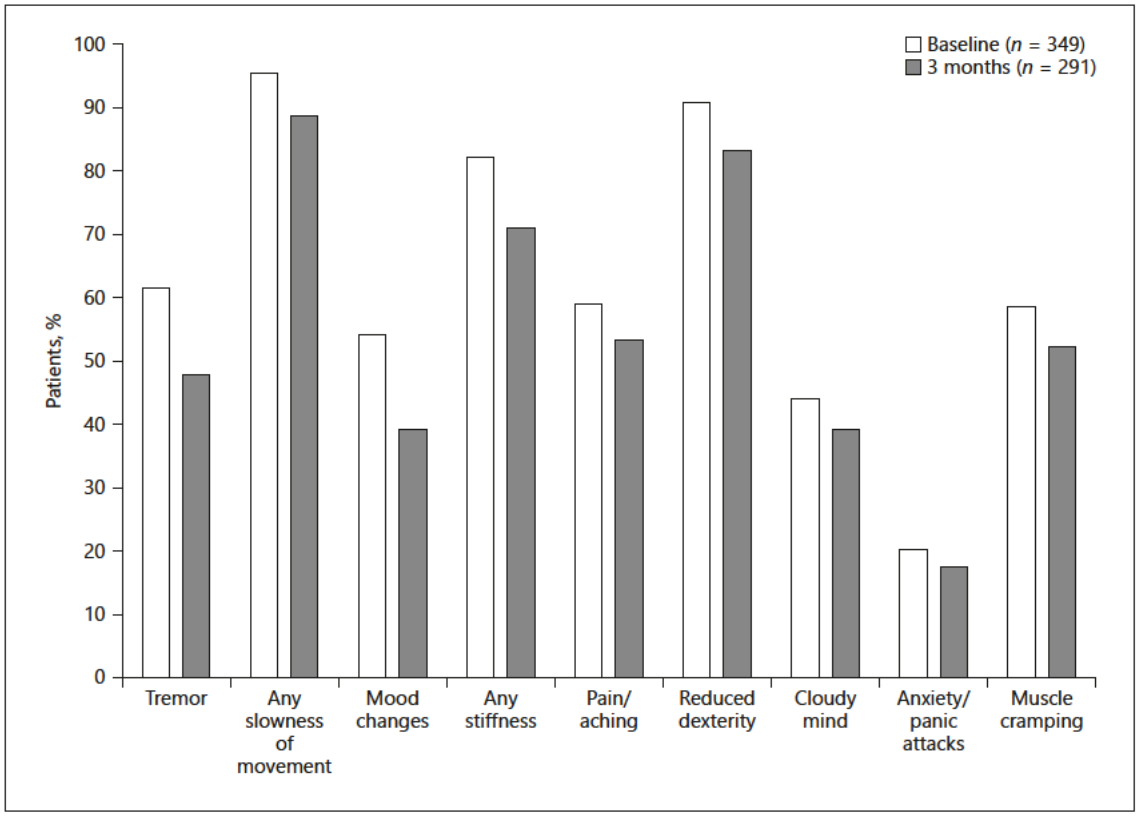

Fig. 3. Presence of Parkinson's disease symptoms as assessed on the WOQ-9. WOQ-9, 9-Symptom Wearing-off Questionnaire.

Presence of Symptoms as Assessed by the WOQ-9

The proportions of patients reporting the overall presence of individual symptoms on the WOQ-9 decreased from baseline to 3 months (Fig. 3). Similar improvements in all nine symptoms were also observed after 1 month of treatment.

Rating Scale Outcomes

Assessments of UPDRS scores after 3 months of opicapone treatment demonstrated no alterations in mentation, behavior and mood (Part I scores) and clinically relevant improvements in activities of daily living (ADL, Part II) during ON and OFF time, motor scores (Part III) during ON time and total scores (Parts II + III) during ON time (Table 2). After 3 months of treatment, UPDRS IV scores were reduced by 0.9 ± 1.8 points.

Patients' quality of life (as assessed by the PDQ-8) and non-motor symptoms (as assessed by the NMSS) were also improved after 3 months of opicapone treatment. A mean ± SD improvement of −3.1 ± 12.5 points and −7.7 ± 18.6 points was observed for PDQ-8 and NMSS, respectively. Improvements to cognition and sleep quality among patients were reported, with a mean ± SD of −1.4 ± 6.09 and −1.2 ± 6.14, respectively.

Levodopa Dosing

After 3 months of opicapone treatment, most patients remained on the same total daily levodopa dose (no change: 88.7%; increase: 6.5%; decrease: 4.8%) and levodopa dosing frequency (no change: 79.7%; increase: 10.0%; decrease: 10.3%), resulting in an overall mean change of approximately −4 mg/day. For patients who reported dopaminergic adverse events (full analysis set), most patients (67.2%) remained on the same total daily levodopa dose, 13.4% received a higher dose and 19.4% a lower dose, resulting in an overall mean change of −23.9 mg/day.

Safety and Tolerability

Overall, 252 (69.4%) patients reported TEAEs, which were mostly mild or moderate (Table 3). Few patients (8.0%) experienced serious TEAEs, including one death due to endocarditis that was considered unrelated to

Table 2. Scale assessments

Scale	
UPDRS Part I (mentation, behavior and mood); mean ± SD	
Baseline (*n* = 349)	2.4±2.1
3 months (*n* = 291)	1.9±1.9
Change from baseline (*n* = 291)	−0.4±1.5
UPDRS Part II (ADL during OFF); mean ± SD	
Baseline (*n* = 348)	16.8±6.8
3 months (*n* = 288)	13.1±6.4
Change from baseline (*n* = 288)	−3.3±4.5
UPDRS Part II (ADL during ON); mean ± SD	
Baseline (*n* = 348)	11.3±6.2
3 months (*n* = 290)	9.0±5.2
Change from baseline (*n* = 289)	−2.0±3.4
UPDRS Part III (motor scores during ON); mean ± SD	
Baseline (*n* = 349)	27.1±12.6
3 months (*n* = 291)	21.2±11.1
Change from baseline (*n* = 291)	−5.3±7.9
UPDRS Total scores (Part II + III); mean ± SD	
Baseline (*n* = 349)	38.4±17.4
3 months (*n* = 291)	30.2±15.2
Change from baseline (*n* = 291)	−7.3±10.1
UPDRS Part IV (complications of therapy); mean ± SD	
Baseline (*n* = 349)	5.0±2.6
3 months (*n* = 291)	3.9±2.4
Change from baseline (*n* = 291)	−0.9±1.8
PDQ-8 Total score; mean ± SD	
Baseline (*n* = 348)	29.4±16.6
3 months (*n* = 291)	25.5±16.0
Change from baseline (*n* = 291)	−3.1±12.5
NMSS Score; mean ± SD	
Baseline (*n* = 349)	42.9±30.5
3 months (*n* = 291)	34.1±26.1
Change from baseline (*n* = 291)	−7.7±18.6

ADL, activities of daily living; NMSS, Non-Motor Symptoms Scale; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-8, Parkinson's Disease Questionnaire; SD, standard deviation.

Table 3. Incidence of treatment emergent adverse events

	N = 363
TEAE category	
Any TEAE	252 (69.4)
Any treatment-related* TEAE	137 (37.7)
Any serious TEAE	29 (8.0)
Any treatment-related* serious TEAE	5 (1.4)
Any TEAE leading to discontinuation	54 (14.9)
Any treatment-related* TEAE leading to discontinuation	40 (11.0)
Any serious TEAE leading to discontinuation	5 (1.4)
Any TEAE leading to death	1 (0.3)
Treatment-related TEAEs (≥2% patients)	
Dyskinesia	21 (5.8)
Dizziness	19 (5.2)
Dry mouth	16 (4.4)
Nausea	14 (3.9)
Constipation	11 (3.0)
Hallucination	8 (2.2)
TEAEs leading to discontinuation (≥1% patients)	
Nausea	8 (2.2)
Constipation	5 (1.4)
Hallucination	4 (1.1)
Dizziness	4 (1.1)

TEAE, treatment emergent adverse event. * Treatment-related TEAEs were any TEAEs that were considered at least possibly related by the investigator and include the events with missing relationship assessment.

treatment. A total of 137 (37.7%) patients reported TEAEs that were at least possibly related to treatment. Similar to the pivotal studies, the most frequent TEAEs (>5%) considered possibly treatment-related were dyskinesia (5.8%), dizziness (5.2%) and dry mouth (4.4%); diarrhea was reported in 3 (0.8%) patients. Serious TEAEs considered at least possibly treatment-related were reported in 5 (1.4%) of patients and TEAEs leading to premature termination occurred in 40 (11.0%) patients. The most common TEAEs leading to withdrawal were nausea (2.2%) and constipation (1.4%). Of note, no dyskinesia led to treatment interruption or discontinuation. There were no relevant changes in vital signs, and physical and neurological examinations throughout the study.

Discussion

PD is the second most common neurodegenerative disorder globally, and its prevalence is expected to rise with the aging population [28]. In Germany, nearly 300,000 people aged 50 years or over have been diagnosed with PD, and the number of hospitalizations for the treatment of PD in the country continues to rise [28, 29].

Currently, levodopa is the standard treatment offered to patients with PD; however, continued use of levodopa monotherapy has been associated with wearing-off symptoms, such as motor fluctuations or dyskinesia [12, 30]. The limited half-life and bioavailability of levodopa has resulted in the investigation of various strategies to optimize levodopa treatment, including the introduction of COMT inhibitors such as opicapone [7, 31].

This sub-analysis of the OPTIPARK study is the first study to confirm the effectiveness, safety and tolerability of once-daily opicapone 50 mg in patients with PD and motor fluctuations in routine clinical practice across

Germany. The majority of patients demonstrated clinical improvements 3 months after starting treatment, in line with the findings previously reported in the primary OPTIPARK study, with 70.8% of patients in the German cohort showing clinical improvement on the CGI-C compared with 71.3% of patients in the overall OPTIPARK population [23]. Treatment with opicapone 50 mg was also generally well tolerated in this patient group, with frequency and type of adverse events as expected for a dopaminergic therapy in patients with PD.

Treatment with opicapone was also associated with an improvement in overall quality of life, as assessed using the PDQ-8. Despite optimized anti-PD therapy (according to clinicians' judgment) and the fact that most (80.7%) patients received levodopa plus another PD medication, UPDRS motor and ADL scores improved (by 5.3 and 3.3 points, respectively). These data are comparable to findings in the original OPTIPARK cohort, which reported UPDRS motor and ADL score increases of 4.6 and 3.0, respectively [23]. Effects of this magnitude have been reported to be clinically relevant [32–34] and may therefore indicate that treatment with opicapone not only increases ON time, but also improves the quality of ON time. Consistent with previous studies in patients with PD [15, 16], this sub-analysis also suggested an overall improvement in non-motor symptoms, such as cognition and sleep quality, which are an important source of disability and a contributor to worse quality of life [35, 36].

The majority of adverse events experienced in this patient cohort were mild to moderate in severity. As reported for the overall patient population of the OPTIPARK study, adverse events were the most common reason for withdrawal from the study and the rate of serious TEAEs considered at least possibly related to treatment was low.

Strengths of this study lie in its size, broad inclusion criteria and routine practice setting. Although this study permitted inclusion of a broad range of disease severities (Hoehn and Yahr stages 1–4), we did not capture sufficient data in this pragmatic study to analyze by subgroups. Other weaknesses include those inherent to open-label studies without placebo control, where both the clinician and patient have expectations from treatment. However, despite these limitations, these real-world data complement evidence from clinical trials and confirm that opicapone added to levodopa in patients with PD and motor fluctuations is effective and generally well tolerated in routine clinical practice across Germany.

Conclusions

This study demonstrates the effectiveness, safety, and tolerability of once-daily opicapone 50 mg in patients with PD and motor fluctuations in real-world settings in Germany. Patients' and clinicians' perceptions about the global PD condition of patients included in this German cohort were improved with the addition of opicapone 50 mg as adjunct therapy to levodopa. In line with findings from the original OPTIPARK study cohort, opicapone was generally well tolerated, ameliorated motor and non-motor symptoms, and improved quality of life. These findings confirm the clinical utility of opicapone 50 mg as an effective adjunct therapy option for the management of motor fluctuations in levodopa-treated patients with PD in routine clinical practice across Germany.

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Statement of Ethics

This study protocol was reviewed and approved by Ethics Committees at all the multiple participating sites. The lead Ethics Committee was at the Technical University Dresden, Dresden, Germany, reference number EK 353082016. 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.

Conflict of Interest Statement

H.R. reports acting on advisory boards, gave lectures, and received research grants from Abbvie, BIAL, Desitin, Eisai, Kyowa Kirin, Novartis, TEVA, UCB Pharma, and Zambon. K.E. reports acting on advisory boards, gave lectures, and received research grants from Abbvie, Acorda, Adamas, Addex, Alkahest, Apopharma, Benevolent, Bial, Biogen, Biohaven, Biotie, Desitin, Impax, Kyowa Kirin, Novartis, Pfizer, Retrotope, Roche, Stada, UCB, and Zambon. C.O. held lectures and created posters for BIAL. T.W. reports acting on advisory boards, gave lectures, and received research grants from AbbVie, Archimedes, Bayer, Bial, Biogen, Desitin, Kyowa, Licher, Pfizer, Phagenesis, Stada, Teva, UCB, and Zambon. A.L. is funded by the Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, University College London, and reports consultancies from Britannia Pharmaceuticals and BIAL. He also reports grants and/or research support from the Frances and Renee Hock Fund and honoraria from Britannia Pharmaceuticals, Profile Pharma, UCB, Roche, BIAL, STADA, NordicInfu Care, and NeuroDerm. M.K. and P.S.S. are employed by BIAL – Portela & C[a], S.A.

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Author Contributions

H.R., K.E., C.O., T.W., and A.L. were study investigators of the primary study and were involved in the study design, data collection, and data interpretation. P.S.S. and M.K. participated in the study design, data collection, data management, and data analysis. All authors provided critical review of the manuscript and approved the final draft.

Data Availability 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.

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