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Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations
A Randomized Clinical Trial

Andrew J. Lees, MD; Joaquim Ferreira, MD; Olivier Rascol, MD; Werner Poewe, MD; José-Francisco Rocha, BSc; Michelle McCrory, MSc; Patricio Soares-da-Silva, MD; for the BIPARK-2 Study Investigators

IMPORTANCE Catechol *O*-methyltransferase (COMT) inhibitors are an established treatment for end-of-dose motor fluctuations associated with levodopa therapy in patients with Parkinson disease (PD). Current COMT inhibitors carry a high risk for toxic effects to hepatic cells or show moderate improvement. Opicapone was designed to be effective without the adverse effects.

OBJECTIVE To evaluate the efficacy and safety of 25- and 50-mg/d dosages of opicapone compared with placebo as adjunct to levodopa therapy in patients with PD experiencing end-of-dose motor fluctuations.

DESIGN This phase 3 international, multicenter outpatient study evaluated a 25- and a 50-mg/d dosage of opicapone in a randomized, double-blind, 14- to 15-week, placebo-controlled clinical trial, followed by a 1-year open-label phase during which all patients received active treatment with opicapone. Patients with PD who experienced signs of end-of-dose deterioration and had a mean total awake off-time (state of akinesia or decreased mobility) of at least 1.5 hours, not including morning akinesia, were enrolled. Data were collected from March 18, 2011, through June 25, 2013. Data from the evaluable population were analyzed from July 31, 2013, to July 31, 2014.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome of the double-blind phase was the change from baseline in absolute off-time vs placebo based on patient diaries. The open-label phase focused on maintenance of treatment effect in off-time.

RESULTS A total of 427 patients (258 men [60.4%] and 169 women [39.6%]; mean [SD] age, 63.1 [8.8] years) were randomized to a 25-mg/d (n = 129) or a 50-mg/d (n = 154) dosage of opicapone or to placebo (n = 144). Of these, 376 patients completed the double-blind phase and entered the open-label phase, of whom 286 completed 1 year of open-label treatment. At the end of the double-blind phase, the least squares mean change (SE) in off-time was −64.5 (14.4) minutes for the placebo group, −101.7 (14.9) minutes for the 25-mg/d opicapone group, and −118.8 (13.8) minutes for the 50-mg/d opicapone group. The adjusted treatment difference vs placebo was significant for the 50-mg/d opicapone group (treatment effect, −54.3 [95% CI, −96.2 to −12.4] minutes; *P* = .008), but not for the 25-mg/d opicapone group (treatment effect, −37.2 [95% CI, −80.8 to 6.4] minutes; *P* = .11). The off-time reduction was sustained throughout the open-label phase (−126.3 minutes at 1-year open-label end point). The most common adverse events in the opicapone vs placebo groups were dyskinesia, constipation, and dry mouth. Fifty-one patients (11.9%) discontinued from the study during the double-blind phase.

CONCLUSIONS AND RELEVANCE Treatment with a 50-mg once-daily dose of opicapone was associated with a significant reduction in mean daily off-time in levodopa-treated patients with PD and motor fluctuations, and this effect is maintained for at least 1 year. Opicapone was safe and well tolerated.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The BIPARK-2 study investigators are listed at the end of this article.

Corresponding Author: Patricio Soares-da-Silva, MD, Department of Research and Development, BIAL–Portela & Ca SA, A Avenida da Siderurgia Nacional, Postal Code 4745-457 Sao Mamede do Coronado, Portugal (psoares.silva@bial.com).

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Catechol *O*-methyltransferase (COMT) inhibitors are an established treatment for motor fluctuations associated with levodopa therapy. Two COMT inhibitors are currently available for clinical use. Tolcapone was widely used, but owing to the risk for potentially fatal hepatic toxic effects, its clinical use now requires regular liver function monitoring and is only considered in patients who have failed to respond to entacapone.[1,2] Entacapone is considered safer, but gains in daily on-time (the state of adequate control of symptoms) are moderate (mean of 0.6 hours across randomized trials[3]). Thus, a more effective COMT inhibitor that can be easily used in routine clinical practice is needed.[4]

Opicapone was rationally designed to provide high COMT inhibitory potency and avoid toxic effects to cells.[5] Opicapone has a very high binding affinity that translates into a slow complex dissociation rate constant and a long duration of action that allows once-daily dosing.[6]

Key Points

Question How effective and safe is opicapone when given as adjunct to levodopa therapy in patients with Parkinson disease who experience motor fluctuations?

Findings In this randomized clinical trial of 427 patients, a 50-mg/d but not a 25-mg/d dosage of opicapone was associated with a significant reduction in off-time vs placebo (treatment effect, −54.31 minutes). This off-time reduction was sustained throughout the 1-year open-label extension study.

Meaning The efficacy and safety of a 50-mg/d dosage of opicapone compares well with currently available catechol *O*-methyltransferase inhibitors.

Methods

Study Conduct

This randomized clinical double-blind placebo-controlled trial evaluated the efficacy and safety of opicapone (25 and 50 mg once daily) as adjunct to levodopa therapy, followed by a 1-year open-label phase during which all patients received opicapone. The study was conducted from March 18, 2011, through June 25, 2013. The double-blind phase was conducted at 71 centers across 12 countries (region 1: Belgium, United Kingdom, and Israel; region 2: Estonia, Czech Republic, and Russia; region 3: South Africa, Australia, and South Korea, region 4: India; region 5: Argentina and Chile), and the open-label phase was conducted at 64 sites (excluding those in the Czech Republic). Institutional review boards at the participating sites approved the protocol (available in Supplement 1); a list of institutional review boards is available in eTable 1 in Supplement 2), and the trial was conducted in accordance with the declaration of Helsinki[7] and International Conference on Harmonization Good Clinical Practice Guidelines.[8] All patients provided written informed consent.

Study Population

Adult men or women (aged 30-83 years) were eligible if they had a clinical diagnosis of Parkinson disease (PD)[9] for at least 3 years, a Hoehn-Yahr stage[10] of 1 to 3 (on stage, or mild unilateral disease to mild to moderate bilateral disease), and at least a 1-year history of clinical improvement with levodopa and/or dopa decarboxylase inhibitor (levodopa/DDCI) therapy. Patients had to have received a stable optimized regimen of 3 to 8 daily doses of levodopa/DDCI therapy and other PD medications for at least 4 weeks before screening. All patients had signs of end-of-dose deterioration for at least 4 weeks before screening, with a mean total awake off-time (state of akinesia or decreased mobility) of at least 1.5 hours, excluding morning akinesia. Patients had to keep reliable diaries; only patients who had filled-in self-rating diary charts in accordance with instructions and had no more than 3 errors per day in the 3 days before the baseline visit were randomized.

Key exclusion criteria included a dyskinesia disability score greater than 3 on item 33 of the Unified Parkinson's Disease Rating Scale (UPDRS) (range, 0-4, with higher scores indicating severely or completely disabling dyskinesia),[11] severe and/or unpredictable off-periods, previous surgery or deep brain stimulation for PD, history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis, or any medical condition that might interfere with assessments, including dementia, clinically significant cardiovascular disease, or psychiatric illness. Patients with a history of liver disease or who had abnormal levels of liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) more than 2 times the upper normal limit at the screening visit were also excluded. Concomitant stable treatment for PD was allowed, with the exception of entacapone, tolcapone, and apomorphine hydrochloride (withdrawn ≥1 month before screening). Treatment with neuroleptics, venlafaxine hydrochloride, monoamine oxidase inhibitors (except selegiline hydrochloride, ≤10 mg/d in oral formulation or 1.25 mg/d in buccal formulation, and rasagiline mesylate, ≤1 mg/d), or antiemetics with antidopaminergic action (except domperidone) was prohibited during the study (withdrawn ≥1 month before screening).

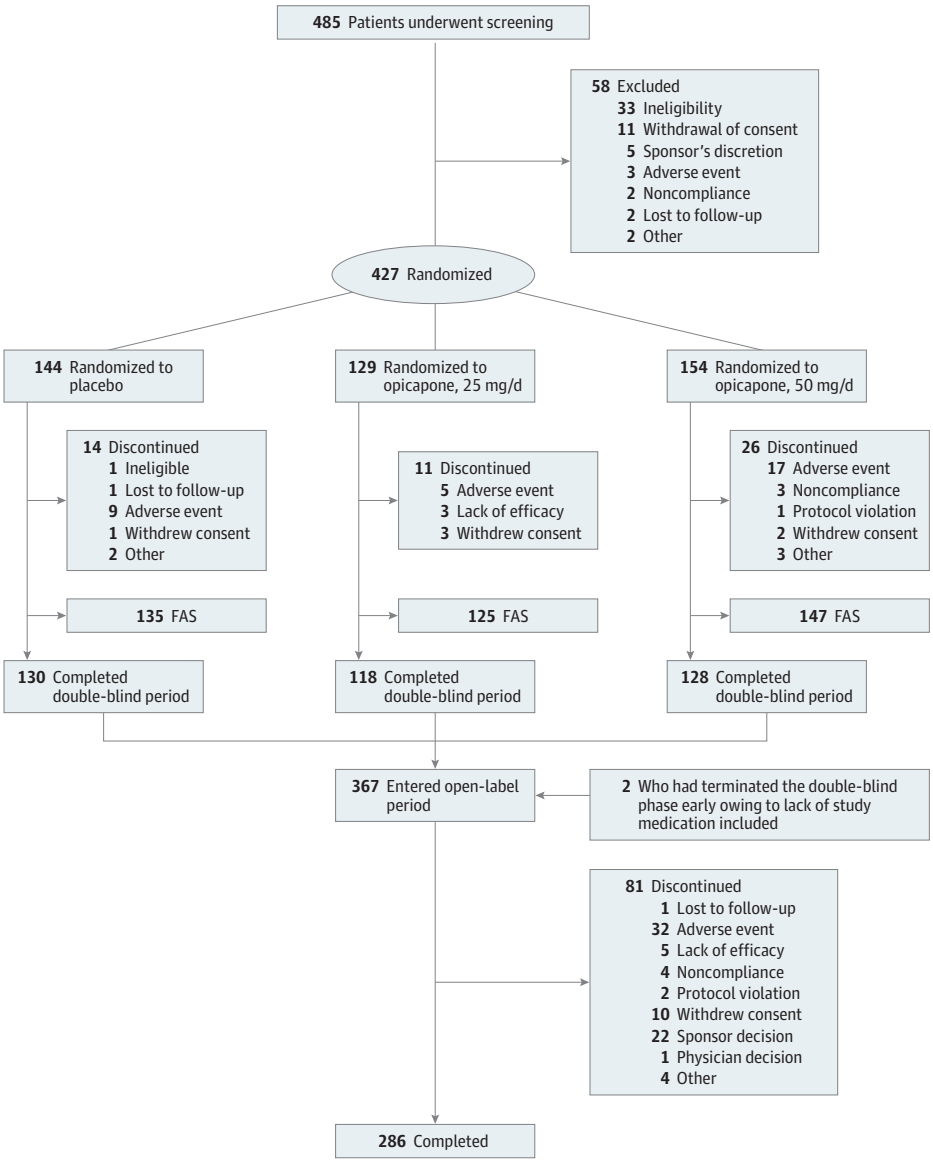
Study Design

Eligible patients were randomized at baseline to the double-blind phase using a computer-generated scheme (administered by Cenduit, LLC) in a ratio of 1:1:1 to the addition of oral opicapone, 25 mg/d or 50 mg/d, or matching placebo using blocks stratified by region (**Figure**). Depending on the need for levodopa/DDCI therapy adjustment, the first efficacy assessment could occur from 3 to 4 weeks after baseline. Thereafter, double-blind assessments occurred at 4-week intervals, and the total duration of the double-blind phase could be 14 to 15 weeks. The open-label phase began the day after completing the double-blind phase and continued until the patient had completed 52 weeks of open-label treatment.

Study Medications

Study medication was taken in the evening, at least 1 hour after the last dose of levodopa/DDCI. In the double-blind phase, reductions in the daily dose (but not frequency) of levodopa/DDCI could be made between baseline and 3 to 4 weeks after

Figure. Study CONSORT Diagram



FAS indicates full-analysis set.

baseline according to the clinical response but were not permitted thereafter. Patients started open-label treatment with the 25-mg/d dosage of opicapone, which could be titrated up to 50 mg/d if greater symptomatic control was required. If unacceptable dopaminergic adverse events appeared, investigators could first lower the levodopa dosage and then, if this was not sufficient, the opicapone dosage could be reduced. Doses of levodopa and opicapone had to remain stable during the last month of study.

Assessments

Primary and key secondary efficacy variables were assessed using 24-hour patient diaries[12] in which patients recorded their status as off, on with troublesome dyskinesia, on with nontroublesome dyskinesia, on without dyskinesia, or asleep for every 30-minute interval during the day for 3 consecutive days before each visit. Patients were trained to identify whether a 30-minute period was spent as mostly on or mostly off. Off- and on-times at each visit were calculated as the mean of the 3 preceding diary days. The proportion of off- and on-time responders per treatment group (proportion of patients with a decrease of ≥1 hour off-time or an increase of ≥1 hour on-time) was also analyzed. Patients also underwent assessment in the on state using the UPDRS,[11] with part II (activities of daily living) completed in the on and off states. Additional outcome measures were the Parkinson's Disease Sleep Scale (PDSS),[13] the 39-item Parkinson's Disease Questionnaire (PDQ-39),[14] the Non-Motor Symptoms Scale (NMSS),[15] and the clinician's and patient's Clinical Global Impression of Change (CGI-C and PGI-C, respectively).[16]

An independent Data Safety Monitoring Board periodically received partially blinded safety data (an unblinded

biostatistician attended meetings to answer any questions). Adverse events, vital signs, and safety laboratory tests were assessed throughout the study. In addition, the Columbia-Suicide Severity Rating Scale[17] and the Modified Minnesota Impulsive Disorders Interview[18] were also assessed.

Statistical Analyses

Data were analyzed from July 1, 2013, to July 1, 2014. Populations undergoing analysis included the double-blind full-analysis set of all randomized patients who took at least 1 dose of study medication and had at least 1 postbaseline off-time assessment; the open-label full-analysis set of all patients who received at least 1 dose of study treatment in the open-label period and had at least 1 off-time efficacy assessment in the open-label period; and the safety set of all patients who received at least 1 dose of study medication.

The primary efficacy variable for the double-blind phase was the change from baseline in absolute off-time, which was analyzed in the double-blind full-analysis set using an analysis of covariance with treatment group and region included as factors and baseline off-time as a covariate. A Dunnett α level adjustment was used for the comparison of each active dose group with placebo, and the last observation carried forward method was used to handle missing diary data.

To avoid inflation of type I errors, key secondary end points in the double-blind phase were analyzed according to the following predefined hierarchy: the proportions of patients achieving at least a 1-hour reduction in absolute off-time and the proportions of patients achieving at least a 1-hour increase in absolute on-time at the end of the double-blind phase; change from baseline to the end of the double-blind phase in UPDRS motor scores; and change from baseline to the end of the double-blind phase in absolute total on-time and percentage of off-time. A nonsignificant result in any of these hierarchical tests meant that all tests performed below that point were considered exploratory. Other scale-based efficacy outcomes were the change from baseline to the end of the double-blind phase in UPDRS, PDSS, PDQ-39, and NMSS scores and the mean CGI-C and PGI-C scores at the end of the double-blind phase. The proportion of off- and on-time responders per treatment group was compared using a Cochran-Mantel-Haenszel test with pooled country as strata. The CGI-C and PGI-C scores were analyzed using a nonparametric van Elteren test[19] for treatment effect stratified by pooled country. Other secondary outcomes were analyzed in a similar manner to the primary efficacy variable.

Maintenance of treatment effect during the open-label phase was analyzed through the change from the start to the end of the open-label phase of absolute off-time using a linear model with pooled country included as a factor. All safety analyses were descriptive and performed using the safety set.

Determination of Sample Size

Assuming that the mean reductions in off-time would be 90 and 105 minutes for the opicapone dosages and 30 minutes for the placebo dosage,[20] a total of 135 evaluable patients in each arm of the double-blind full-analysis set was estimated to ensure at least 95% power to confirm a treatment effect vs placebo in the most efficacious opicapone dosage group and at least 85% power to confirm a treatment effect in the least efficacious opicapone dosage group.

Results

Patient Disposition

Of the 485 patients screened, 427 were enrolled and randomized (258 men [60.4%] and 169 women [39.6%]; mean [SD] age, 63.1 [8.8] years). Of these, 376 (88.1% of randomized patients) completed the double-blind phase (Figure). Overall, 367 patients who completed the double-blind phase, including 2 patients who had discontinued the double-blind phase early owing to lack of study medication, entered the open-label phase, and 286 of these (77.9%) completed 1 year of open-label treatment. The most common reason for study discontinuation in both phases was adverse events.

Demographics, Baseline Characteristics, and PD Medications

Most baseline characteristics were comparable between groups (**Table 1**); however, the placebo group had slightly fewer male and more Asian patients compared with the active treatment groups. Patients had a mean (SD) disease duration (time since diagnosis) ranging from 7.7 (3.7) to 8.5 (4.4) years and had been receiving levodopa for a mean (SD) of 6.8 (3.6) to 7.2 (4.3) years. The mean (SD) daily levodopa dose was 700 (312) to 806 (398) mg and the mean (SD) duration of wearing off was 3.0 (2.3) to 3.2 (3.3) years.

Primary Efficacy Analysis in the Double-Blind Phase

All groups achieved reductions in off-time vs baseline (eFigure in Supplement 2). At the end of the double-blind phase, the mean (SD) change in off-time was −64.5 (14.4) minutes for the placebo group, −101.7 (14.9) minutes for the 25-mg/d opicapone group, and −118.8 (13.8) minutes for the 50-mg/d opicapone group. The adjusted least squares mean change from baseline in absolute off-time at study end was largest in the 50-mg/d opicapone group. The adjusted treatment difference compared with the placebo group was significant for the 50-mg/d opicapone group (treatment effect [SD], −54.3 [18.9] minutes; 95% CI, −96.2 to −12.4 minutes; $P = .008$), but not for the 25-mg/d opicapone group (treatment effect [SD], −37.2 [19.6] minutes; 95% CI, −80.8 to 6.4 minutes; $P = .11$).

Secondary Outcomes in the Double-Blind Phase

Secondary efficacy findings are summarized in **Table 2**. Compared with the placebo group with off-time response rates of 68 (50.4%) and on-time response rates of 61 (45.2%), the proportion of responders in the full-analysis set was significantly higher among the off-time responders in the 25-mg/d opicapone group (78 [62.4%]; $P = .04$) and 50-mg/d opicapone group (97 [66.0%]; $P = .009$) and among on-time responders in the 25-mg/d opicapone group (79 [63.2%]; $P = .004$) and the 50-mg/d opicapone group (91 [61.9%]; $P = .006$). Under the hierarchical procedure, the next key secondary variable to be analyzed was the change from baseline to the end of double-blind phase in UPDRS motor scores. Mean

Table 1. Demographics and Baseline Disease Characteristics at Entry to the Double-Blind Phase

Parameter	Treatment Group, Mean (SD)		
		Opicapone Dosage	
	Placebo (n = 135)	25 mg/d (n = 125)	50 mg/d (n = 147)
Male, No. (%)	71 (52.6)	82 (65.6)	89 (60.5)
Age, y	61.5 (8.9)	62.5 (8.5)	65.5 (8.4)
Race/ethnicity, No. (%)			
White[a]	89 (65.9)	90 (72.0)	115 (78.2)
Asian	42 (31.1)	29 (23.2)	31 (21.1)
Other	3 (2.2)	6 (4.8)	1 (0.7)
Time since PD diagnosis, y	7.7 (3.7)	8.5 (4.4)	8.2 (4.5)
Time since levodopa therapy initiation, y	6.8 (3.6)	7.2 (4.3)	7.1 (4.7)
Time since onset of wearing off, y	3.0 (2.3)	3.2 (2.8)	3.2 (3.3)
Modified Hoehn-Yahr stage (on)[b]	2.4 (0.6)	2.3 (0.7)	2.4 (0.5)
Total UPDRS score[c]	31.5 (17.0)	30.8 (16.9)	31.7 (17.6)
UPDRS Part III (motor) score[d]	22.5 (12.0)	21.5 (12.0)	22.5 (12.3)
Off-time			
Absolute time, h	6.1 (2.3)	6.2 (2.2)	6.3 (2.2)
Total awake time, %	37.5 (13.8)	38.8 (13.2)	38.9 (12.8)
On-time without or with nontroublesome dyskinesia			
Absolute time, h	9.6 (2.4)	9.2 (2.3)	9.4 (2.2)
Total awake time, %	59.0 (14.5)	57.4 (12.9)	57.9 (13.0)
On-time with troublesome dyskinesia			
Absolute time, h	0.6 (1.4)	0.6 (1.3)	0.5 (1.2)
Total awake time, %	3.5 (8.7)	3.8 (8.5)	3.2 (7.2)
Presence of dyskinesia, No. (%)	72 (53.3)	65 (52.0)	80 (54.4)
Levodopa dosage, mg/d	714 (338)	806 (398)	700 (312)
DDCI used with levodopa, No. (%)[e]			
Carbidopa	83 (61.5)	87 (69.6)	91 (61.9)
Benserazide	60 (44.4)	43 (34.4)	65 (44.2)
Adjunct medications, No. (%)[f]			
Dopamine agonist	98 (72.6)	83 (66.4)	102 (69.4)
Monoamine oxidase type B inhibitor	26 (19.3)	23 (18.4)	32 (21.8)
Anticholinergic	13 (9.6)	20 (16.0)	14 (9.5)
Amantadine	29 (21.5)	29 (23.2)	28 (19.0)

Abbreviations: DDCI, dopa decarboxylase inhibitor; PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Data were missing for one patient in the placebo group.

[b] Stages range from 0 to 5, with higher stages indicating worse motor function.

[c] Scores range from 0 to 176, with higher scores indicating worse symptom severity.

[d] Scores range from 0 to 108, with higher scores indicating worse motor symptom severity.

[e] Some patients used both formulations.

[f] Patients could receive multiple adjunct medications.

(SE) changes in motor function were small and similar across all groups (−2.1 [0.5] for the placebo group; −2.9 [0.5] for the 25-mg/d opicapone group [P = .26]; −2.0 [0.5] for the 50-mg/d opicapone group [P = .82]); thus, according to the hierarchical procedure, all analyses from this point were considered exploratory.

Other diary-reported secondary efficacy findings supported those of the primary analysis and confirmed that treatment with opicapone resulted in larger increases in mean (SE) least squares absolute on-time (58.7 [14.2] minutes in the placebo group, 104.1 [14.7] minutes in the 25-mg/d opicapone group [P = .02], and 111.3 [13.7] minutes in the 50-mg/d opicapone group [P = .005]) and larger reductions in the mean (SE) least squares percentage of off-time (−6.7% [1.4%] in the placebo group, −11.0% [1.5%] in the 25-mg/d opicapone group [P = .03], and −12.1% [1.4%] in the 50-mg/d opicapone group [P = .004]) (Table 2). Most of the gain of on-time with opicapone was without troublesome dyskinesia; increases in on-time with troublesome dyskinesia were not significantly different from the placebo group (11.2 minutes) for the 25-mg/d opicapone group (19.4 minutes; P = .49) or the 50-mg/d opicapone group (25.6 minutes; P = .21) (eTable 2 in Supplement 2). The UPDRS total (reduction of −3.5 to −4.4 points), UPDRS activities of daily living in the off state (reduction of −1.9 to −2.5 points), UPDRS activities of daily living in the on state (reduction of −0.5 to −1.0 points), PDSS (increase of 2.3 to 5.1 points), PDQ-39 (reduction of −2.6 to −4.8 points), NMSS (reduction of −2.0 to −5.2 points), CGI-C (increase of 3.2 to 3.5 points), and PGI-C (increase of 3.2 to 3.5 points) assessments showed some improvements across all treatment groups, with no significant differences among them.

Maintenance of Treatment Effect in the Open-Label Phase

Off-time reduction from the double-blind baseline was sustained during the open-label phase; the adjusted mean change from the start to the end of the open-label phase in off-time was −18.31 (95% CI, −43.56 to 6.95) minutes. Mean (SD) total on-time increased by 24.9 (156.4) minutes, and this increase

Table 2. Key Secondary Efficacy Results in Hierarchical Order in Double-Blind Phase

Variable	Treatment Group		
		Opicapone Dosage	
	Placebo (n = 135)	25 mg/d (n = 125)	50 mg/d (n = 147)
Key Secondary End Points in Hierarchical Order			
Responder rate of off-time reduction of ≥1 h at end of double-blind phase			
No. (%)	68 (50.4)	78 (62.4)	97 (66.0)
OR (95% CI)	NA	1.7 (1.0 to 2.8)	1.9 (1.2 to 3.1)
P value vs placebo	NA	.04	.009
Responder rate of on-time increase of ≥1 h at end of double-blind phase			
No. (%)	61 (45.2)	79 (63.2)	91 (61.9)
OR (95% CI)	NA	2.1 (1.3 to 3.4)	2.0 (1.2 to 3.2)
P value vs placebo	NA	.004	.006
Change from baseline to end of double-blind phase in UPDRS Part III scores			
LS, mean (SE)	−2.1 (0.5)	−2.9 (0.5)	−2.0 (0.5)
Treatment effect vs placebo (95% CI)	NA	−0.8 (−2.3 to 0.6)	1.6 (−1.2 to 1.5)
P value	NA	.26	.82
Change from baseline to end of double-blind phase in absolute total on-time, min[a]			
LS, mean (SE)	58.7 (14.2)	104.1 (14.7)	111.3 (13.7)
Treatment effect vs placebo (95% CI)	NA	45.4 (7.1 to 83.8)	52.6 (15.8 to 89.3)
P value	NA	.02	.005
Change from baseline to end of double-blind phase in off-time, %[b]			
LS, mean (SD)	−6.7 (1.4)	−11.0 (1.5)	−12.1 (1.4)
Treatment effect vs placebo (95% CI)	NA	−4.3 (−8.2 to −0.4)	−5.5 (−9.2 to −1.7)
P value	NA	.03	.004
Scale-Based Outcome Measures From Baseline to End of Double-Blind Phase			
UPDRS total score[c]			
No. of patients	122	114	127
LS, mean (SE)	−3.5 (0.7)	−4.4 (0.7)	−3.5 (0.7)
P value vs placebo	NA	.37	.45
UPDRS Part II (ADL) score (off)[d]			
No. of patients	122	114	127
LS, mean (SE)	−1.9 (0.4)	−2.5 (0.4)	−2.2 (0.3)
P value vs placebo	NA	.24	.56
UPDRS Part II (ADL) score (on)[d]			
No. of patients	122	114	127
LS, mean (SE)	−1.0 (0.3)	−1.1 (0.3)	−0.5 (0.2)
P value vs placebo	NA	.69	.18
PDSS score[e]			
No. of patients	133	123	147
LS, mean (SE)	5.1 (1.8)	2.5 (1.9)	2.3 (1.7)
P value vs placebo	NA	.29	.23
PDQ-39 score[f]			
No. of patients	118	112	124
LS, mean (SE)	−4.8 (1.0)	−2.6 (1.0)	−4.4 (1.0)
P value vs placebo	NA	.12	.78
NMSS score[g]			
No. of patients	126	121	147
LS, mean (SE)	−5.2 (1.6)	−2.0 (1.6)	−4.9 (1.5)
P value vs placebo	NA	.13	.88
CGI-C score[h]			
No.	134	124	146
Mean (SD)	3.4 (0.3)	3.2 (0.3)	3.5 (0.2)
P value vs placebo	NA	.11	.83
PGI-C score[h]			
No.	134	124	146
Mean (SD)	3.4 (1.2)	3.2 (1.4)	3.5 (1.3)
P value vs placebo	NA	.08	.82

Abbreviations: ADL, activities of daily living; CGI-C, clinician's Clinical Global Impression of Change; LS, least squares; NA, not applicable; NMSS, Non-Motor Symptoms Scale; OR, odds ratio; PDQ-39, Parkinson's Disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; PGI-C, patient's Clinical Global Impression of Change; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Considered exploratory outcome under the hierarchical analysis. On-time was assessed as the sum of all on-time (including on with troublesome dyskinesia, with nontroublesome dyskinesia, and without dyskinesia).

[b] Calculated as the sum in minutes from 30-minute periods classified as off divided by the total time awake.

[c] Scores range from 0 to 176, with higher scores indicating worse symptom severity.

[d] Scores range from 0 to 52, with higher scores indicating greater effect.

[e] Scores range from 0 to 150, with higher scores indicating lower disability due to sleep problems.

[f] Scores range from 0 to 100, with higher scores indicating worse perceived health status.

[g] Scores range from 0 to 360, with higher scores indicating greater disability due to nonmotor symptoms.

[h] Scores range from 1 to 7, with 1 indicating very much improved; 2, much improved, 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse.

was again mostly owing to an increase of on-time without or with nontroublesome dyskinesia. During the open-label phase, mean (SD) on-time with troublesome dyskinesia increased by 6.0 (129.1) minutes.

Levodopa Dosage Reductions

At the end of the permitted adjustment period (first 2-3 weeks of the double-blind phase), the overall levodopa dose decreased by a mean of 47.2 mg in the 25-mg/d opicapone group and 29.3 mg in the 50-mg/d opicapone group compared with 9.4 mg in the placebo group. At the end of the double-blind phase, the mean levodopa doses were 762.5 mg in the 25-mg/d opicapone group, 674.3 mg in the 50-mg/d opicapone group, and 713.3 mg in the placebo group.

During the open-label phase, the mean daily levodopa dose was maintained below the baseline value, with 213 of 339 patients (62.8%) continuing to receive the same dose of levodopa. The mean (SD) number of daily levodopa doses also remained stable during this phase, ranging from 4.69 (1.54) to 4.76 (1.56) during the course of the year. Overall, 40 of 339 patients (11.8%) had a reduction of the levodopa dose between the open-label baseline and the end of study. At the end of the open-label phase, the mean levodopa dose was 693.9 mg, a decrease of 35.6 mg vs the double-blind baseline.

Safety and Tolerability

More than half of patients in each group (total, 282 of 411 patients [68.6%]) experienced at least 1 adverse event (**Table 3**), which was usually mild or moderate in intensity. In the double-blind phase, the most common adverse events occurring in the opicapone groups compared with the placebo group were dyskinesia, constipation, and dry mouth. Most of the dyskinesia events (58 [75.3%]) across all groups occurred in patients already experiencing dyskinesia at baseline. Serious adverse events were observed in 18 patients (4.4%) in the double-blind phase and in 40 of 353 patients (11.3%) in the open-label phase (Table 3). One death (due to pneumonia in the placebo group) occurred in the double-blind phase and 5 deaths (due to septic shock, small cell lung cancer, cerebral hemorrhage after traumatic brain injury, cerebral hemorrhage, and an unknown cause) occurred in the open-label phase.

In the double-blind phase, discontinuations due to adverse events were more frequent for the 50-mg/d opicapone group (17 of 150 [11.3%]) than for the 25-mg/d opicapone group (5 of 125 [4.0%]) or the placebo group (9 of 136 [6.6%]) (**Table 4**). The most common adverse event leading to study discontinuation was dyskinesia (4 patients in the 50-mg/d opicapone group; 1 patient in the placebo group; and none in the 25-mg/d opicapone group). Other adverse events leading to study discontinuation were reported in 26 patients (6.1%); no patient discontinued study participation owing to diarrhea. Thirty-two patients (9.1%) discontinued because of an adverse event during the open-label phase. In this phase, the most common treatment-related reasons for study discontinuations were dopaminergic events (3 patients [0.8%] for dyskinesia, 3 [0.8%] for hallucinations, and 1 [0.3%] for orthostatic hypotension) and aggravation of PD (2 [0.5%]).

No relevant liver function findings occurred in either phase. The Columbia-Suicide Severity Rating Scale showed no effect on suicidality. Impulsive disorders as screened with the Modified Minnesota Impulsive Disorders Interview were reported in few patients.

Table 3. Summary of Treatment-Emergent Adverse Events in Open-Label Phase

Type of Adverse Event	No. (%) of Patients
All	
≥1	268 (75.9)
Serious	40 (11.3)
Leading to discontinuation	32 (9.1)
Death	5 (1.4)
Affecting >5% in any arm	
Dyskinesia	76 (21.5)
PD aggravated	60 (17.0)
Fall	32 (9.1)
Blood creatine phosphokinase level increased	26 (7.4)
Insomnia	20 (5.7)
Orthostatic hypotension	19 (5.4)

Abbreviation: PD, Parkinson disease.

Table 4. Summary of Treatment-Emergent Adverse Events in Double-Blind Phase

	No. (%) of Patients		
		Opicapone Dosage	
Type of Adverse Event	Placebo (n = 136)	25 mg/d (n = 125)	50 mg/d (n = 150)
All			
≥1	87 (64.0)	87 (69.6)	108 (72.0)
Serious	5 (3.7)	4 (3.2)	9 (6.0)
Leading to discontinuation	10 (7.4)	5 (4.0)	18 (12.0)
Death	1 (0.7)	0	0
Affecting >5% in any arm			
Dyskinesia	11 (8.1)	30 (24.0)	36 (24.0)
Constipation	2 (1.5)	12 (9.6)	10 (6.7)
Dry mouth	1 (0.7)	13 (10.4)	6 (4.0)
Blood creatine phosphokinase level increased	5 (3.7)	5 (4.0)	12 (8.0)
PD aggravated	7 (5.1)	9 (7.2)	6 (4.0)
Fall	9 (6.6)	7 (5.6)	7 (4.7)
Hypertension	3 (2.2)	8 (6.4)	6 (4.0)
Nausea	8 (5.9)	8 (6.4)	5 (3.3)
Headache	9 (6.6)	6 (4.8)	6 (4.0)
Insomnia	3 (2.2)	10 (8.0)	2 (1.3)
Urinary tract infection	2 (1.5)	3 (2.4)	9 (6.0)

Abbreviation: PD, Parkinson disease.

Discussion

In this phase 3 study, once-daily treatment with opicapone was well tolerated and was associated with significant therapeutic benefits in patients with PD who experienced motor fluctuations, despite current treatment with levodopa and other adjunct PD medications. The change from baseline in absolute off-time at the end of the double-blind phase showed a significant improvement compared with placebo in the 50-mg/d opicapone group, and the benefits of off-time reduction were sustained throughout the 1-year open-label phase. Although we found greater reductions of off-time with the 25-mg/d opicapone group, the treatment differences were not significant compared with the placebo group. This finding may result from the higher-than-expected placebo effects that occurred in this study. The sample size of 135 patients per arm was calculated under the assumption of a much lower placebo response (30 minutes) than was actually achieved (64.5 minutes), suggesting that the study may have been underpowered to detect differences between groups.

The present results are similar to those of another phase 3 study,[21] which also showed that treatment with opicapone effectively reduced off-time and increased on-time without increasing the frequency of troublesome dyskinesia. In that study, the 50-mg/d dosage was also demonstrated to be noninferior to adjunct entacapone treatment, which was included as an active comparator.[21] Likewise, the reductions in off-time seen in the present study also compare well with those of other studies[22-25] of adjunct therapy for motor complications in PD. Patients receiving the 50-mg/d dosage had a mean off-time reduction of 54.3 minutes vs placebo, which is higher than the mean of 0.6 hour (36 minutes) reported for the entacapone studies (which had broadly similar study designs to this study),[3] and which is more similar to off-time reductions reported for other adjuvant treatments such as dopamine agonists.[3,26] The similarity of the phase 3 opicapone trial designs will allow meta-analyses of effect sizes to be performed, facilitating our understanding the efficacy of opicapone in all outcome measures.

Although UPDRS motor function and other scale-based measures, including nonmotor symptoms and quality of life, all improved during the double-blind phase, we found no significant differences between groups. This result may be because the patients were already receiving levodopa treatment for symptomatic control and the study was only designed and powered to address a potential differentiation in motor fluctuations. By the end of the open-label phase, mean PDSS, NMSS, and PDQ-39 scores maintained an overall improvement relative to the double-blind baseline scores (eTable 3 in Supplement 2). Because patients with PD and motor fluctuations often require frequent medication changes, it is noteworthy that most patients maintained the levodopa dose and dosing frequency from the end of the titration phase throughout the duration of the study, which can be considered an additional indicator of sustained control of motor fluctuations during the long term.

Opicapone was well tolerated with no apparent dose-relationship for the most of the adverse events. In the double-blind phase, the most common adverse events associated with opicapone treatment (dyskinesia, constipation, and dry mouth) reflected greater dopaminergic availability. Toxic effects to the liver have prevented the clinical use of tolcapone and development of other COMT inhibitors. We therefore are reassured that no relevant liver issues were observed with opicapone. Similarly, diarrhea has been considered a class effect of COMT inhibition,[27,28] but this adverse event was absent from both phases of the study, and no cases of severe diarrhea were reported with opicapone treatment. The continued tolerability of the drug during the open-label phase is supported by the low rate of patients who prematurely withdrew because of an adverse event (32 patients).

Conclusions

Treatment with opicapone effectively reduced off-time and increased on-time without increasing the frequency of troublesome dyskinesia, and this benefit was maintained for at least 1 year of therapy without increasing the levodopa dose. The magnitude of treatment effect with the 50-mg/d dosage of opicapone is considered clinically relevant,[29] with approximately 1 hour of reduction in off-time. The simplicity afforded by the once-daily administration means that addition of this drug will not further complicate the patients' current drug regimen, while allowing more sophisticated adjustments to the levodopa regimen that are harder to achieve, in practice, when giving levodopa in a combined pill with a COMT inhibitor (even taking into consideration the number of dose availabilities for the combined pill). When combined with the favorable safety and tolerability profile, these characteristics position opicapone as a strong candidate for the adjunct treatment of motor fluctuations in PD.

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Author Affiliations: Reta Lila Weston Institute, University College London, London, England (Lees); Centro de Estudos Egas Moniz, Hospital de Santa Maria, Lisbon, Portugal (Ferreira); Department of Clinical Pharmacology, Institut National de la Santé et de la Recherche Medicale (INSERM) and University Hospital of Toulouse, Toulouse, France (Rascol); Department of Neurosciences, INSERM and University Hospital of Toulouse, Toulouse, France (Rascol); Department of Neurology, Innsbruck Medical University, Innsbruck, Austria (Poewe); Department of Research and Development, BIAL–Portela & Ca SA, Sao Mamede do Coronado, Portugal (Rocha, Soares-da-Silva); Quintiles, Dublin, Ireland (McCrory); Department of Pharmacology and Therapeutics, University Porto, Porto, Portugal (Soares-da-Silva).

Author Contributions: Ms McCrory and Dr Soares-da-Silva had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lees, Ferriera, Rascol, Poewe, Soares-da-Silva.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lees.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: McCrory, Soares-da-Silva.
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Study supervision: Lees, Ferreira, Rocha, Soares-da-Silva.

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Group Information: The following lead investigators of the BIPARK-2 Study Investigators participated in this study: *Argentina:* Ruben Alfredo Femmini (Consultans Medicina Institute), Nelida Susana Garretto (Instituto Argentino de Investigacion), Rolando Giannaula (Hospital Español), Federico Eduard Micheli (Instituto Frenopatico SA), Maria Peralta (Fundacion Alfredo Thomson), Edguardo Gabriel Reich (Instituto Medico Especializado), and Gustavo Angel Saredo (Centro de Investigaciones Clinicas del Litoral SRL); *Australia:* Denis Crimmins (Central Coast Neuroscience Research), Andrew Evans (Royal Melbourne Hospital), Andrew Hughes (Austin Repatriation General Hospital), Thomas Kimber (Royal Adelaide Hospital), Katya Kotschet (St Vincent's Hospital), Neil Mahant (Westmead Hospital), Dominic Thyagarajan (Monash Medical Centre), and Stephen Tisch (St Vincent's Hospital); *Belgium:* Philip Bourgeois (Heilig Hart Ziekenhuis), Nina De Klippel (Jessa Ziekenhuis–Campus Virga Jesse), Anne Jeanjean (Cliniques Universitaires Saint-Luc), Barbara Ann Pickut (UZ Antwerpen), and Philippe Tack (St Andries Ziekenhuis); *Chile:* Pedro Chana (CETRAM), Marcelo De Giorgis (Clinica Ciudad del Mar), Daniel Galdames (Hospital Dr. Sotero del Rio), Carlos Juri (Hospital Clinico Pontificia Universidad), Manuel Lavados (Especialidades Medicas L y S), Luis Lay-son (Hospital Barros Luco Trudeau), Marcelo Leiva (Hospital Base Valdivia), and Pablo Venegas (Avenida Apoquindo 4100); *Czech Republic:* Jiri Novak (Neurologicka ambulance CK), Ladislav Pazdera (CTC Rychnov nad Kneznou, SRO), Simoneta Soukupova (Euromed Praha), and Katerina Zarubova (Neurologie-EEG, SRO); *Estonia:* Katrin Gross-Paju (West Tallinn Central Hospital), Ande Lindmäe (West Tallinn Central Hospital), Pille Taba (Tartu University Hospital), and Toomas Toomsoo (East Tallinn Central Hospital); *India:* Samsher Dwivedee (Vidya Sagar Institute of Mental Health and Neuroscience), Pahari Ghosh (Sri Aurobindo Seva Kendra), Uday Murgod (Manipal Hospital), Shankar Nellikunja (Mallikatta Neuro and Research Centre), Vijaya Pamidimukkala (Lalitha Super Speciality Hospital), Hemant Sant (Sahyadri Hospital), Jitender Singh (Gurukrupa Hospital and Research Centre), and Krishnan Vijayan (Kovai Medical Center and Hospital Limited); *Israel:* Ruth Djaldetti (Rabin Medical Center-Beilinson Campus), Sharon Hassin (Chaim Sheba Medical Center), Illana Schlesinger (Rambam Health Care Campus), and Tanya Gurevich (Tel Aviv Sourasky Medical Centre); *Russia:* Valentina Alifirova (Siberian State Medical University), Elena Arefieva (SIH Kemerovo Regional Clinical Hospital), Alexander Fedyanin (State Healthcare Institution "Territorial Clinical Hospital"), Dimitry Pokhabov (Krasnoyarsk State Medical Academy), and Elena Vostrikova (SEIHPE Novosibirsk State Medical University of Roszdrav); *South Africa:* J. A. Carr (Tygerberg Hospital), Christo C. Coetzee (Dr CC Coetzee Inc, Netcare Umhlanga Medical Centre), Nyda Fourie (Iatros SA), Andrew Frost (Vincent Pallotti Hospital), M. Kakaza (University of Pretoria Clinical Trial Unit), Simon Kesler (Claremont Hospital), Stan Lipschitz (The Memory Centre), David Lurie (Sunninghill Hospital), Johan Smuts (Willows Medical Centre), and Leon van der Spuy (Western Cape Clinical Trials); *South Korea:* Jin Whan Cho (Samsung Medical Center), Sun-ju Chung (Asan Medical Center), Jae Woo Kim (Dong-A University Medical Center), and Young Ho Sohn (Severance Hospital, Yonsei University College of Medicine); and *United Kingdom:* Bernard Boothman (Fylde Coast Hospital), David Burn (Clinical Ageing Research Unit, Newcastle University Campus for Ageing and Vitality), Donald Grosset (Southern General Hospital), Sophie Molloy (Charing Cross Hospital), Nicola Pavese (Charing Cross Hospital), and Richard Weiser (Morriston Hospital).

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