Efficacy and Safety of Once-Daily Opicapone 50 mg in Patients with Parkinson's Disease and Motor Fluctuations: Pooled Analysis of Two Randomized, Double-Blind, Placebo-Controlled Studies

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INTRODUCTION

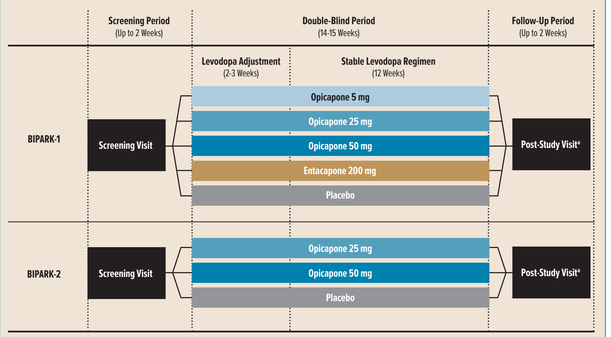
- Levodopa/carbidopa is the most effective treatment for managing the signs and symptoms of Parkinson's disease (PD), but both levodopa-induced dyskinesia and motor fluctuations/OFF periods are important clinical concerns[1]
- Since levodopa is metabolized in the periphery by catechol-O-methyltransferase (COMT), sustained inhibition of COMT can improve levodopa treatment outcomes by decreasing variability in circulating levodopa concentrations, thereby reducing OFF-time[2-4]
- Limitations of currently approved COMT inhibitors include pill burden, tolerability issues, and/or safety risks requiring frequent monitoring[5,6]
- Opicapone is a once-daily COMT inhibitor[7,8] under United States Food and Drug Administration review as an adjunct to levodopa/carbidopa for PD patients experiencing OFF episodes
- The efficacy, safety, and tolerability of once-daily opicapone in PD patients with motor fluctuations on a stable regimen of levodopa/dopa decarboxylase inhibitor have been evaluated in 2 double-blind (DB), placebo-controlled, pivotal Phase 3 clinical trials, BIPARK-1 (NCT01568073)[9] and BIPARK-2 (NCT01227655)[10]
- This presentation evaluates the efficacy, safety, and tolerability of adjunctive opicapone using pooled data from BIPARK-1 and BIPARK-2 participants

METHODS

STUDY DESIGN

- BIPARK-1 and BIPARK-2 were multinational, multicenter, randomized, DB, placebo-controlled, parallel-group studies (**Figure 1**)
  - In BIPARK-1, participants were randomized (1:1:1:1:1) to DB treatment with opicapone (5, 25, or 50 mg), entacapone (200 mg), or placebo for 14–15 weeks as adjunct to their current levodopa regimen
  - In BIPARK-2, participants were randomized (1:1:1) to DB treatment with opicapone (25 or 50 mg) or placebo for 14–15 weeks as adjunct to their current levodopa regimen
  - In both studies, other PD medications were allowed with stable dosing regimens, and the Investigator could adjust the levodopa dose during the first 2–3 weeks according to participant response, not exceeding baseline level

Figure 1. Study Designs



[a]Participants who completed each double-blind study were eligible to continue into respective open-label extension studies; post-study visits were completed in participants who did not continue.

PARTICIPANTS

- Key inclusion criteria:
  - Men or women, ages 30 to 83 years, with a clinical diagnosis of idiopathic PD for ≥3 years
  - Modified Hoehn and Yahr (H&Y) stage of 1–3 in ON-state
  - ≥1 year of treatment with levodopa with clinical improvement
  - Motor fluctuations with a mean OFF-time per day of ≥1.5 hours (not including pre-dose morning akinesia)
  - Ability to keep accurate 24-hour diaries
- Key exclusion criteria:
  - Dyskinesia disability score >3 on the Unified Parkinson's Disease Rating Scale item 33
  - Severe and/or unpredictable OFF periods
  - Previous or planned stereotactic surgery for PD (including deep brain stimulation)
  - Previous use of entacapone (BIPARK-1 only)

ANALYSES

- Efficacy data from BIPARK-1 (excluding entacapone and opicapone 5 mg) and BIPARK-2 were pooled and analyzed using a mixed model for repeated measures
- In the pooled Full Analysis Set (FAS), changes from baseline in absolute OFF-time were analyzed by study visit (Weeks 1, 2/3, 6/7, and 10/11) and at the end of DB treatment (Week 14/15)
- The mean change from baseline to Week 14/15 in absolute OFF-time was also analyzed in the following exploratory subgroups:
  - Age: <65 years, ≥65 years
  - Gender: men, women
  - Race: white, Asian
  - Modified H&Y stage in ON-state: <2.5, ≥2.5
  - Concurrent medication use: dopamine agonist (DA: yes, no); monoamine oxidase-B inhibitor (MAOBI: yes, no)
- Safety data from BIPARK-1 (excluding entacapone) and BIPARK-2 DB periods were pooled and analyzed descriptively
- In the pooled safety population, assessments included treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), laboratory tests, vital signs, and electrocardiograms (ECGs)

RESULTS

- Demographics and PD characteristics were generally comparable across treatment groups (**Table 1**)

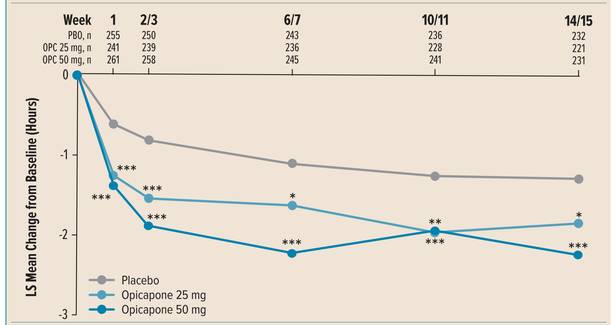
Table 1. Demographics and Baseline Characteristics (Safety Population)

	Placebo (n=257)	Opicapone 5 mg (n=122)	Opicapone 25 mg (n=244)	Opicapone 50 mg (n=265)
Demographics				
Age, mean (SD), years	62.8 (9.1)	63.6 (9.3)	63.4 (8.8)	64.5 (8.8)
Men, n (%)	142 (55.3)	71 (58.2)	149 (61.1)	160 (60.4)
White, n (%)	211 (82.1)	122 (100)	209 (85.7)	231 (87.2)
Asian, n (%)	42 (16.3)	0 (0)	29 (11.9)	33 (12.5)
PD Characteristics				
Disease duration, mean (SD), years	7.7 (3.9)	7.5 (3.6)	7.9 (4.3)	7.6 (4.3)
Motor fluctuation duration, mean (SD), years	2.6 (2.2)	2.3 (2.3)	2.7 (2.7)	2.7 (2.9)
Presence of dyskinesia, n (%)	122 (47.5)	57 (46.7)	115 (47.1)	133 (50.2)
Daily OFF-time, mean (SD), hours[a]	6.1 (2.1)	6.7 (2.1)	6.5 (2.2)	6.3 (2.0)
UPDRS III in ON-state, mean (SD)	24.8 (12.1)	28.7 (12.3)	25.3 (13.1)	25.1 (13.2)
Daily levodopa dose, mean (SD), mg	695 (321)	646 (311)	732 (370)	698 (322)
Concurrent Medications, n (%)				
Dopamine agonist	188 (73.2)	71 (58.2)	162 (66.4)	183 (69.1)
Monoamine oxidase-B inhibitor	49 (19.1)	20 (16.4)	49 (20.1)	57 (21.5)

[a]In the pooled FAS population: placebo, n=255; opicapone 5 mg, n=119; opicapone 25 mg, n=241; opicapone 50 mg, n=262.
FAS, Full Analysis Set; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

- In the pooled FAS population, reduction in OFF-time from baseline to Week 14/15 was significantly greater with opicapone 50 mg versus placebo at all study visits (**Figure 2**)
  - At Week 14/15, least squares mean changes (± standard error) were -2.22 (±0.17) hours for opicapone 50 mg (P<0.001) and -1.28 (±0.17) hours for placebo

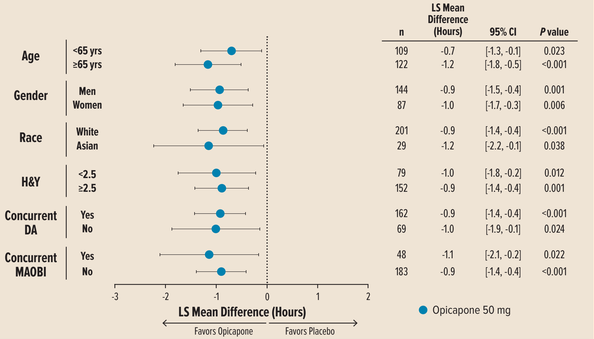
Figure 2. Change from Baseline in Absolute OFF-Time by Study Visit (FAS)



Nominal *P<0.05, **P<0.01, ***P<0.001 versus placebo.
FAS, Full Analysis Set; LS, least squares; OPC, opicapone; P80, placebo.

- Supportive of the pooled FAS results, the exploratory subgroup analyses indicated that opicapone 50 mg significantly reduced daily OFF-time relative to placebo regardless of age, gender, race, disease stage, or concurrent PD medication use (**Figure 3**); no statistically significant or qualitative treatment-by-subgroup interactions were observed

Figure 3. Effects of Opicapone on Absolute OFF-Time at Week 14/15 (FAS Subgroups)



		n	LS Mean Difference (Hours)	95% CI	*P* value
Age	<65 yrs	109	-0.7	[-1.3, -0.1]	0.023
	≥65 yrs	122	-1.2	[-1.8, -0.5]	<0.001
Gender	Men	144	-0.9	[-1.5, -0.4]	0.001
	Women	87	-1.0	[-1.7, -0.3]	0.006
Race	White	201	-0.9	[-1.4, -0.4]	<0.001
	Asian	29	-1.2	[-2.2, -0.1]	0.038
H&Y	<2.5	79	-1.0	[-1.8, -0.2]	0.012
	≥2.5	152	-0.9	[-1.4, -0.4]	0.001
Concurrent DA	Yes	162	-0.9	[-1.4, -0.4]	<0.001
	No	69	-1.0	[-1.9, -0.1]	0.024
Concurrent MAOBI	Yes	48	-1.1	[-2.1, -0.2]	0.022
	No	183	-0.9	[-1.4, -0.4]	<0.001

CI, confidence interval; DA, dopamine agonist; FAS, Full Analysis Set; H&Y, Hoehn & Yahr; LS, least squares; MAOBI, monoamine oxidase-B inhibitor; n, number of participants in the active treatment group.

- The overall incidence of TEAEs was slightly higher with opicapone 50 mg than with placebo, but few patients in either treatment arm had a serious TEAE or discontinued due to a TEAE (**Table 2**)
  - Dyskinesia was the most common TEAE, but few participants had serious dyskinesia (opicapone 50 mg, 0.4%; placebo, 0%) or dyskinesia leading to discontinuation (opicapone 50 mg, 3.0%; placebo, 0.4%)
  - AESIs (e.g., falls) occurred in ≤5% of participants in any treatment arm

Table 2. Adverse Events (Safety Population)

	Placebo (n=257)	Opicapone 5 mg (n=122)	Opicapone 25 mg (n=244)	Opicapone 50 mg (n=265)
Summary, n (%)				
Any TEAE	147 (57.2)	63 (51.6)	152 (62.3)	170 (64.2)
Any serious TEAE	11 (4.3)	4 (3.3)	5 (2.0)	13 (4.9)
Any TEAE leading to discontinuation[a]	19 (7.4)	7 (5.7)	14 (5.7)	24 (9.1)
Deaths[b]	1 (0.4)	0	0	0
Common TEAEs, n (%)[c]				
Dyskinesia	16 (6.2)	17 (13.9)	39 (16.0)	54 (20.4)
Constipation	5 (1.9)	4 (3.3)	12 (4.9)	17 (6.4)
Insomnia	4 (1.6)	2 (1.6)	17 (7.0)	9 (3.4)
Dry mouth	3 (1.2)	2 (1.6)	16 (6.6)	8 (3.0)
Common AESIs, n (%)				
Fall	12 (4.7)	2 (1.6)	11 (4.5)	8 (3.0)
Somnolence	5 (1.9)	1 (0.8)	10 (4.1)	5 (1.9)

[a]Includes 3 participants who had a TEAE that started during the double-blind period and resulted in discontinuation from the subsequent open-label extension period.
[b]One death in the placebo group due to pneumonia.
[c]Reported in >5% of participants in any treatment group.
AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

- Other TEAEs associated with COMT inhibitors were not commonly reported with opicapone 50 mg versus placebo, including diarrhea (2.3% versus 1.9%) and chromaturia (0% versus 0%)
- No notable mean changes from baseline were found in vital signs, ECGs, or laboratory parameters, including liver function tests, in all treatment groups

CONCLUSIONS

- In the pivotal Phase 3 studies, BIPARK-1 and BIPARK-2, levodopa-treated adults with PD and motor fluctuations had a significant reduction in daily OFF-time with opicapone 50 mg (targeted therapeutic dose) versus placebo
- Significant OFF-time improvement with opicapone 50 mg was observed as early as 1 week after treatment initiation, and exploratory analysis indicated significant improvement with opicapone 50 mg regardless of demographic characteristics, PD disease severity, or treatment with other PD medication classes
- Once-daily opicapone up to 50 mg was generally well tolerated in PD patients with motor fluctuations taking stable regimens of levodopa and other allowed PD medications

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