Safety and Tolerability of Opicapone in Patients with Parkinson's Disease and Motor Fluctuations: Pooled Analysis of Two Double-Blind, Placebo-Controlled Phase 3 Studies

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INTRODUCTION

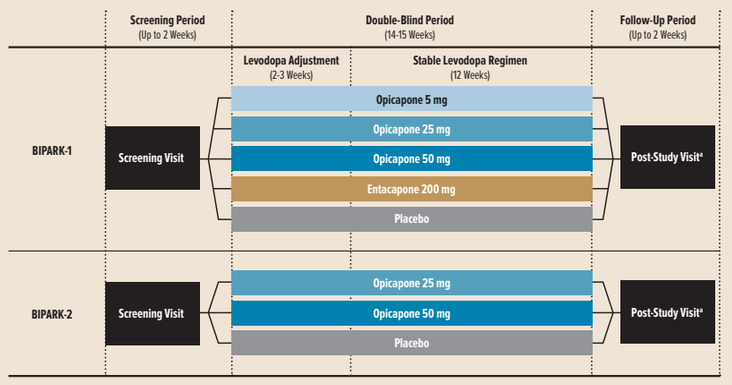
- Levodopa is the most effective treatment for Parkinson's disease (PD), but both levodopa-induced dyskinesia and motor fluctuations with OFF periods are important clinical concerns[1]
- Augmentation therapy with catechol-O-methyltransferase (COMT) inhibitors can improve levodopa treatment outcomes by decreasing variability in circulating levodopa concentrations[2,3]
- COMT inhibitors have been approved in the United States (US) as adjunctive therapies to levodopa, but currently available medications are limited by pill burden, tolerability issues, and/or safety risks requiring frequent monitoring[4,5]
- Opicapone is a highly selective, peripherally acting COMT inhibitor approved in Europe and under development in the US as an adjunct to levodopa to treat PD fluctuations with once-daily administration[6,7]
- 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 two double-blind (DB), placebo-controlled, pivotal Phase 3 clinical trials, BIPARK-1 (NCT01568073)[8] and BIPARK-2 (NCT01227655)[9]
- BIPARK-1 and BIPARK-2 had similar patient populations and results; in both studies, once-daily treatment with opicapone 50 mg demonstrated a significant reduction in daily OFF-time compared to placebo[8,9]
- The objective of this analysis is to assess the safety and tolerability of once-daily opicapone using pooled data from BIPARK-1 and BIPARK-2

METHODS

STUDY DESIGNS

- BIPARK-1 and BIPARK-2 were multinational, multicenter, 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
  - Participants who completed each DB study were eligible to continue into the respective open-label extension study

Figure 1. Study Designs



[a]In participants who did not continue into the open-label extension study.

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 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)

ASSESSMENTS AND ANALYSES

- Data from the BIPARK-1 and BIPARK-2 DB periods were pooled and analyzed descriptively
- Entacapone data (from BIPARK-1) were not included in the pooled safety analyses
- Assessments included treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale (C-SSRS), and Modified Minnesota Impulsive Disorders Interview (mMIDI)

RESULTS

- Baseline characteristics were generally similar across treatment groups (**Table 1**)

Table 1. Demographics and Baseline Characteristics

	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)
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)
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)

PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

- Overall, the incidence of TEAEs was slightly higher with opicapone than with placebo (**Table 2**)
  - The incidences of serious TEAEs and discontinuation due to TEAEs were generally low and comparable between opicapone and placebo groups
  - Dyskinesia was the most common TEAE, however, 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%)
  - Serious TEAEs that occurred in >1 participant were dyskinesia and basal cell carcinoma (2 partcipants each [0.3%]); there were no clinically important differences in the types of serious TEAEs reported across the opicapone dose groups
  - Other TEAEs associated with dopaminergic medications and/or COMT inhibitors were not commonly reported, as indicated by the following results for opicapone 50 mg vs. placebo: fall (3.0% vs. 4.7%), somnolence (1.9% vs. 1.9%), diarrhea (2.3% vs. 1.9%), hallucinations (3.4% vs. 1.2%), orthostatic hypotension (1.5% vs. 0%), syncope (1.1% vs. 0.4%), chromaturia (0% vs. 0%), sleep attacks (0% vs. 0.8%), and impulse control disorders (1.1% vs. 0%); few of these events were serious or led to discontinuation

Table 2. Treatment-Emergent Adverse Events

	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)

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

- Mean changes in liver function tests were generally small in all treatment groups, including opicapone 50 mg (**Table 3**)
  - Potentially clinically significant changes in liver function tests occurred in ≤2 participants in any treatment group
- No opicapone-treated participant met Hy's law criteria
- Mean changes in other laboratory parameters were also generally small in all treatment groups

Table 3. Liver Function Tests

Parameter	Mean (SD) Change from Baseline[a]			
	Placebo (n=246)	Opicapone 5 mg (n=117)	Opicapone 25 mg (n=234)	Opicapone 50 mg (n=250)
ALT, U/L	-1.0 (12.6)	0.3 (8.5)	2.6 (25.9)	1.7 (9.4)
AST, U/L	-0.9 (8.3)[b]	1.0 (7.4)	0.4 (10.1)	1.4 (8.1)
ALP, U/L	-0.6 (13.6)	-1.1 (14.8)	-2.0 (11.8)	-2.9 (13.7)
GGT, U/L	1.1 (20.6)	2.4 (14.9)	-1.2 (13.0)[b]	-1.9 (13.4)[b]
Total bilirubin, µmol/L	0.4 (3.4)	0.1 (3.5)	-0.3 (3.1)[b]	-0.5 (3.3)

[a]Based on available assessment.
[b]Based on available assessment: placebo, n=245; opicapone 25 mg, n=235; opicapone 50 mg, n=249.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; SD, standard deviation.

- No notable mean changes from baseline were found in vital signs or ECGs in any treatment group
  - Incidence of threshold orthostatic blood pressure change was 31.4% for opicapone 50 mg and 35.4% for placebo
  - Incidence of QTcF >450 msec was 5.1% for opicapone 50 mg and 2.6% for placebo
  - No participant had a QTcF >500 msec or a change from baseline >60 msec
- Based on available C-SSRS data, most participants had no suicidal ideation at baseline (score=0): opicapone 50 mg, 96.5% (111/115); placebo, 94.7% (126/133)
  - Among these participants, few had an emergence of suicidal ideation at any time during treatment (score=1 to 5): opicapone 50 mg, 0.9% (1/111); placebo, 0.8% (1/126)
- Based on available mMIDI data, the incidence of compulsive behaviors was generally similar at baseline and post-baseline for both placebo and opicapone (all doses) (**Table 4**)

Table 4. Percentage of Participants with mMIDI Compulsive Behaviors[a]

Incidence, % (n/N)	Placebo		Opicapone (All Doses)	
	At Baseline	Post-Baseline	At Baseline	Post-Baseline
Buying disorder	5.1 (4/78)	5.1 (7/137)	9.8 (20/205)	9.3 (30/322)
Pathological gambling	1.3 (1/78)	0.7 (1/137)	2.0 (4/204)	0.9 (3/322)
Compulsive sexual behavior	3.9 (3/76)	2.2 (3/135)	1.5 (3/204)	2.2 (7/317)

[a]Based on item endorsement ("yes") at baseline or during treatment.
mMIDI, Modified Minnesota Impulsive Disorders Interview; n, number of participants with compulsive disorder; N, number of participants with an available assessment.

CONCLUSIONS

- Once-daily opicapone up to 50 mg was generally well tolerated by PD patients with motor fluctuations taking stable regimens of levodopa and other allowed PD medications
- TEAEs associated with other COMT inhibitors (e.g., serious/severe diarrhea and chromaturia) were infrequently reported
- Aside from dyskinesia, other TEAEs of clinical interest (e.g., fall, hallucinations, somnolence) were not commonly reported in opicapone-treated participants
- There were no cases of acute hepatitis or trends in TEAEs or laboratory findings to suggest hepatotoxicity with opicapone treatment
- There was no evidence of increased risk of suicidality or impulse control disorder with opicapone treatment

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Disclosures: These studies were conducted by BIAL-Portela & C[a] SA, Sao Mamede do Coronado, Portugal. This poster was funded by Neurocrine Biosciences, Inc., San Diego, CA. Writing assistance and editorial support were provided by Prescott Medical Communications Group, Inc., Chicago, IL.

PRESENTED AT THE XXIV WORLD CONGRESS ON PARKINSON'S DISEASE AND RELATED DISORDERS
JUNE 16-19, 2019; MONTREAL, CANADA