Long-Term Follow-Up of Opicapone Use As Add-On to Levodopa in Parkinson's Patients Without Motor Fluctuations: Findings From the EPSILON Study

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Background

- Levodopa (L-dopa) is the most effective symptomatic treatment for Parkinson's disease (PD), but its long-term use at high doses is associated with the development of motor complications.[1,2]
- Opicapone (OPC) is a third-generation COMT inhibitor that enhances peripheral levodopa bioavailability[3] and reduces OFF time in PD patients with motor fluctuations.[4,5]
- COMT inhibition in early PD has been discussed as a strategy to enhance L-dopa bioavailability, to improve motor response magnitude, and stabilize dopamine levels, potentially providing more consistent motor benefits and delaying motor complications.[6]

Objective

- To assess the long-term effect of OPC (up to 76 weeks) in enhancing the clinical benefit of oral L-dopa therapy in patients with PD without motor complications.

Methods

Study population

- L-dopa–treated patients (300-500 mg, 3-4 times daily) aged 30-80 years with PD diagnosed ≤5 years and Hoehn & Yahr stage 1-2.5 (ON state) were enrolled.
- Eligible patients had motor disability (MDS-UPDRS Part III ≥20) despite stable anti-PD therapy.
- Patients with prior motor complications (MDS-UPDRS Part IV A + B + C >0) were excluded.

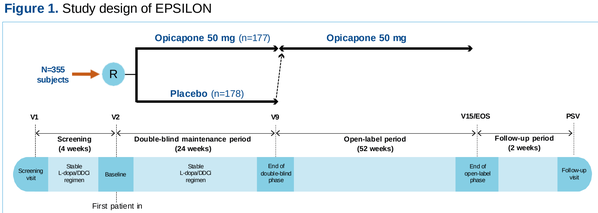
Study design

- EPSILON was a Phase III, double-blind (DB), multicenter, randomized, placebo-controlled trial.
- Patients were randomized (1:1) to OPC 50 mg or placebo for a 24-week DB phase, followed by an optional 52-week open-label (OL) phase where all received OPC 50 mg (**Figure 1**).

Study assessments

- The primary endpoint was the MDS-UPDRS Part III score mean change from baseline to week 24.
- In the OL phase, the key endpoint was the change in MDS-UPDRS Part IV from OL baseline to week 52.
- Safety was assessed by treatment-emergent adverse events (TEAEs).

Figure 1. Study design of EPSILON



DDCi, dopa decarboxylase inhibitor; EOS, end of study; L-dopa, levodopa; PSV, post-study visit; R, randomization; V, visit

Table 1. Baseline characteristics of patients entering the open-label period

	OPC-OPC n = 151	PLC-OPC n = 155
At double-blind entry		
Mean (SD) age at screening; years	63.9 (9.4)	63.9 (9.7)
Male, n (%)	95 (62.9%)	104 (67.1%)
Mean (SD) time since PD; years	3.0 (1.1)	2.8 (1.2)
Modified Hoehn and Yahr stage, n (%)		
Stage 1-1.5	31 (20.5%)	19 (12.3%)
Stage 2	100 (66.2%)	113 (72.9%)
Stage 2.5	20 (13.2%)	23 (14.8%)
At open-label entry		
Mean (SD) levodopa dose	387 (109)	383 (89)
Levodopa/DDCi alone	53 (35.1%)	68 (43.9%)
Levodopa/DDCi and other anti-PD therapy	98 (64.9%)	87 (56.1%)
Dopamine agonists		
Pramipexole, n (%)	47 (31.1%)	40 (25.8%)
Ropinirole, n (%)	26 (17.2%)	17 (11.0%)
MAO-B inhibitors		
Rasagiline, n (%)	31 (20.5%)	28 (18.1%)
Mean (SD) Levodopa equivalent daily dose (LEDD)	737 (236)	513 (195)

MAO-B, monoamine oxidase-B; OPC, opicapone; PLC, placebo; SD, standard deviation

Results

Patient population

- 355 patients were randomized and the full analysis set in the DB phase included 176 patients in the OPC group and 177 in the PLC group.
- Of 322 patients completing the DB phase, 307 entered open-label OPC treatment (prior-OPC, n=152; prior-placebo, n=155) with similar baseline characteristics **(Table 1)**.
- 246 patients completed the 52-week extension. Most common reason for early discontinuation was study termination in Ukraine (n=21) followed by withdrawal of consent (n=12).

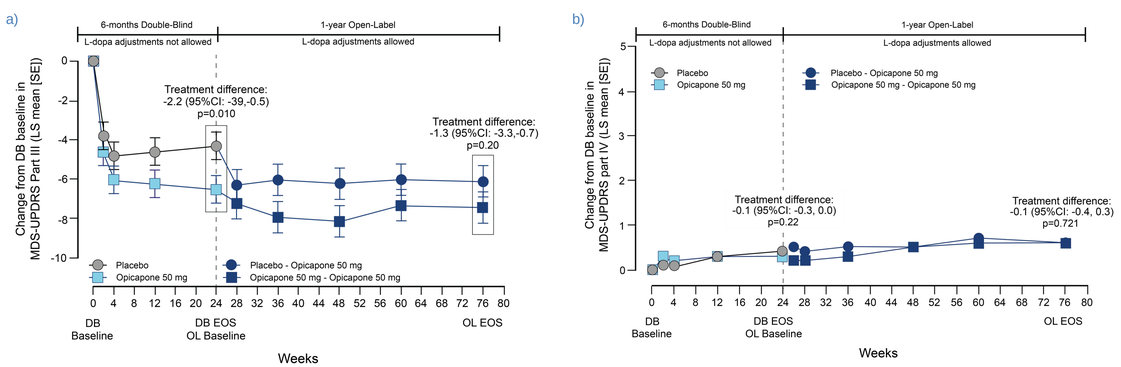
MDS-UPDRS Part III (motor scores)

- At Week 24, OPC significantly improved MDS-UPDRS-III vs placebo (LS mean change: -6.5 vs -4.3; difference: -2.2 [-3.9, -0.5]; p=0.010) (**Figure 2a**).
- Motor improvements were maintained over one year in OPC-OPC patients, with an LS mean change of -7.4±0.81 after 1.5 years and an additional -1.5±0.67 from OL baseline.
- Patients switching from placebo to OPC showed similar improvements, with an LS mean change of -1.7±0.67 from OL baseline and -6.1±0.79 from DB baseline.
- Early OPC initiation provided additional motor benefits, with an adjusted difference of -1.3 [95%CI: -3.3, 0.7]; (p=0.20) at study end.

MDS-UPDRS Part IV (motor complications)

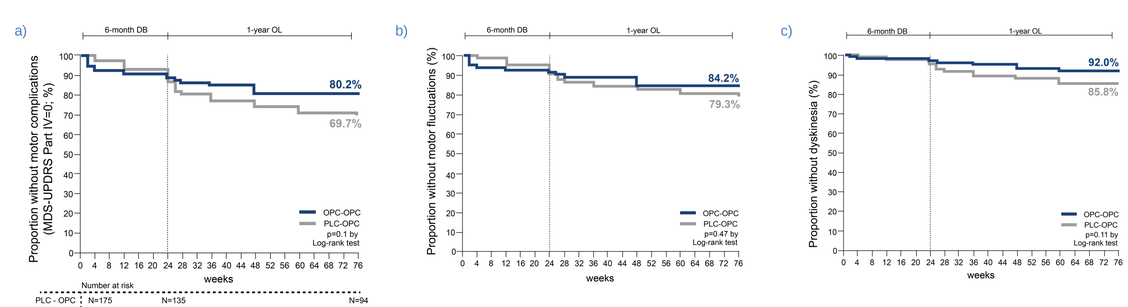
- Earlier and longer OPC exposure did not significantly increase motor complications, as MDS-UPDRS Part IV scores remained low throughout treatment (**Figure 2b**).
- At study end, a higher proportion OPC-OPC patients remained free of motor complication (MDS-UPDRS Part IV score=0) than in the PLC-OPC group (80.2% vs 69.7%, p=0.1, **Figure 3a**).
- No significant differences were observed in the proportion of patients free from fluctuations (84.2% vs 79.3%), dyskinesias (92% vs 85.9%) (**Figure 3 b-c**) or dystonia (95.1% vs 95.7%).

Figure 2. Change from baseline in a) MDS-UPDRS Part III (motor scores) and b) MDS-UPDRS Part IV (motor complications)



The primary and key endpoints were analyzed using a Mixed Model Repeated Measures (MMRM) approach, adjusting for baseline, center, treatment, visit, treatment and baseline by visit interaction, and patient as a random effect. Between-group differences estimated from the model. CI, Confidence interval; DB, double-blind; EOS, end of study; L-dopa, levodopa; LS, Least square; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; OL, open-label; OPC, opicapone; PLC, placebo.

Figure 3. Development of motor complications: Kaplan-Meier survival curves for patients remaining free of (a) motor complications, (b) motor fluctuations, and (c) dyskinesia



Time to motor complications was evaluated using the MDS-UPDRS Part IV score and categorized by type: dyskinesia (item 4.1–time spent with dyskinesia), motor fluctuations (item 4.3–time spent in OFF), DB, double-blind; EOS, end of study; L-dopa, levodopa; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; OL, open-label; OPC, opicapone; PLC, placebo.

Safety and tolerability

- Opicapone was generally well tolerated (**Table 2**).
- TEAEs were more frequent in PLC-OPC than OPC-OPC patients (63.9% vs 53.0%).
- Most common TEAEs were ON-OFF phenomenon (9.7% vs 8.6%) and dyskinesia (9.0% vs 7.0%)

Table 2. Adverse events during open-label treatment with opicapone

	OPC-OPC n = 151	PLC-OPC n = 155
Any TEAE, n (%)	80 (**53.0**)	99 (**63.9**)
Treatment-related TEAE, n (%)	16 (**10.6**)	35 (**22.6**)
Mild	13 (8.6)	27 (17.4)
Moderate	3 (2.0)	7 (4.5)
Severe	0	1 (0.6)
Most common (>2%) **TEAEs**, n (%)		
ON/OFF phenomenon	13 (8.6)	15 (9.7)
Dyskinesia	7 (4.6)	14 (9.0)
Dizziness	3 (2.0)	2 (1.3)
Headache	7 (4.6)	7 (4.5)
Parkinson's disease	6 (4.0)	5 (3.2)
COVID-19	5 (3.3)	5 (3.2)
Urinary tract infection	3 (2.0)	2 (1.3)
Back pain	1 (0.7)	9 (5.8)
Arthralgia	5 (3.3)	2 (1.3)
Fatigue	4 (2.6)	1 (0.6)
Insomnia	5 (3.3)	5 (3.2)
Hypertension	5 (3.3)	0
Fall	6 (4.0)	2 (1.3)
Serious TEAE, n (%)	17 (11.3)	13 (8.4)
TEAE leading to death*, n (%)	5 (3.3)*	0
TEAE leading to withdrawal, n (%)	6 (4.0)	4 (2.6)

* TEAEs leading to death were due to AEs considered unrelated to study treatment.
OPC, opicapone; PLC, placebo, TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In levodopa–treated PD patients without motor complications, adding OPC significantly improved motor impairment when compared with placebo.
- OPC's beneficial motor effect was sustained for over 1.5 years, with most patients remaining free of motor complications.
- Long-term exposure to OPC was well tolerated and with a favorable safety profile.

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Conflicts of interest

JJF has received personal compensation for serving as a Consultant for Abbvie, Bial, Biogen, Lundbeck, and Neurocrine. JJF has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Bial, Biogen, Lundbeck, and Neurocrine. JJF has received personal compensation for serving on a Speakers Bureau for Abbvie, BIAL, Infucare, Nordic, ONO and SK Chemicals. OR has received personal compensation for serving as a consultant for Abbvie, Acorda, Aguettant, Alkahest, AlzProtect, Apopharma, Astrazeneca, Axovant, Bial, Biogen, Britannia, Buckwang, Centogene, Cerevel, Clevexel, Contera, GE Healthcare, Handtherapeutic, Ionis, Ifab, Jazz, Kyowa, LGD Nuvamid, Lundbeck, Merck, Merz, MundiPharma, Neuralight, Neuratris, Neuroderm, Novartis, ONO Pharma, Orion Pharma, Osmotica, Oxford Biomedica, Parexel, PD Neurotechnology, Pfizer, Polycaps, Prexton, Roche, Sanofi, Scienture, Servier, Sombiotech, Sunovion, Supernus, Synagile, Thelonius Mind, Takeda, Theranexus, Teva, Tools4patient, UCB, Vision 2 voice, XenoPort, XO, and Zambon. OR has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Acorda, Aguettant, Alkahest, AlzProtect, Apopharma, Astrazeneca, Axovant, Bial, Biogen, Britannia, Buckwang, Centogene, Cerevel, Clevexel, Contera, GE Healthcare, Handtherapeutic, Ionis, Ifab, Jazz, Kyowa, LGD Nuvamid, Lundbeck, Merck, Merz, MundiPharma, Neuralight, Neuratris, Neuroderm, Novartis, ONO Pharma, Orion Pharma, Osmotica, Oxford Biomedica, Parexel, PD Neurotechnology, Pfizer, Polycaps, Prexton, Roche, Sanofi, Scienture, Servier, Sombiotech, Sunovion, Supernus, Synagile, Thelonius Mind, Takeda, Theranexus, Teva, Tools4patient, UCB, Vision 2 voice, XenoPort, XO, and Zambon. OR has received personal compensation for serving on a Speakers Bureau for Bial and Medizin Academy. The institution of OR has received research support from Agence Nationale de la Recherche (ANR), CHU de Toulouse, France-Parkinson, INSERM-DHOS Recherche Clinique Translationnelle, Michael J. Fox Foundation, Programme Hospitalier de Recherche Clinique, and European Commission (PP7, H2020). FS has received personal compensation for serving as a Consultant for Abbvie, Bial, Biogen, Blue Rock, Britannia, Chiesi, Kyowa, Lundbeck, Lusofarmaco, Neurodem, Roche, Sunovion, Synegile, UCB, and Zambon. FS has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Bial, Biogen, Roche, Sunovion, Synegile, and Zambon. FS has received personal compensation serving on a Speakers Bureau for Bial, Kyowa, Sunovion, UCB, and Zambon. AA has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Bial, Roche, Theravance, UCB. AA has received personal compensation for serving on a Speakers Bureau for Abbvie, Boehringer, and Zambon. PL, HB, JFR, and JH have received personal compensation for serving as employees of Bial. GCF has nothing to disclose. GB has received personal compensation for serving as an employee of Amneal Pharmaceuticals. JH has received personal compensation for serving as an officer or member of the Board of Directors for Bial RD Investments. JH has received personal compensation for serving as an officer or member of the Board of Directors for Bial Portela SA. JH has received personal compensation for serving as an officer or member of the Board of Directors for Bial Biotech. JH has received personal compensation serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Wiley. JH has stock in Astra Zeneca. JH has received intellectual property interests from a discovery or technology relating to health care. WP has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Alterity, Bial, Biogen, Britannia, Denali Pharmaceuticals, Lilly, Lundbeck, Neurocrine, Neuroderm, Roche, Takeda, UCB, and Zambon. WP has received personal compensation for serving on a Speakers Bureau for Abbvie, Bial, Britannia, Lundbeck, STADA, and Zambon. WP has received research support from MJFF EU Horizon Programme. WP has a non-compensated relationship as a Committee member with Movement Disorder Society that is relevant to AAN interests or activities. Study supported by Bial – Portela & Ca, S.A.

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