# Opicapone Improved Parkinson's Disease-related Sleep Disturbances: Findings from the Oasis Study

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## Background

- Sleep disorders are among the most frequent non-motor symptoms in Parkinson's disease (PD), affecting up to 80% of patients at all stages[1–3]
- Levodopa (L-dopa) remains the most effective symptomatic treatment for PD; however, with the progression of PD, its therapeutic window narrows leading to the development of complications such as end-of-dose motor fluctuations and associated non-motor fluctuations such as pain, anxiety and sleep disorders[2,4]
- The catechol-O-methyl transferase (COMT) inhibitor opicapone (OPC) has been shown to be generally well tolerated and efficacious in reducing OFF time in two pivotal Phase 3 studies in patients with PD and end-of-dose motor fluctuations (BIPARK I and II)[5,6]
- Results of the Phase 4 study OPTIPARK suggested that the addition of OPC to L-dopa/dopa decarboxylase inhibitor (DDCI) therapy might have a positive effect on sleep[7]

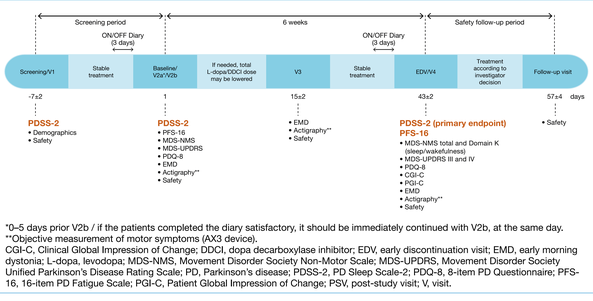
## Objective

The OpicApone in Sleep dISorder (OASIS) exploratory trial aimed to evaluate the effects of OPC on sleep when added to existing L-dopa/DDCI treatment in PD patients with end-of-dose motor fluctuations and associated sleep disorders, not previously treated with COMT inhibitors

## Methods

- OASIS was an exploratory, open-label, single-arm, multicentre study conducted in PD patients with end-of-dose motor fluctuations and associated sleep disorders (**Figure 1**)
  - All patients received OPC 50 mg once daily as an add-on to L-dopa/DDCI therapy for 6 weeks
- Patients were included if they had a diagnosis of idiopathic PD with modified Hoehn & Yahr stage of 1–3 (at ON state), wearing-off signs (daily OFF time of ≥1.5 hour), PD-associated sleep disorders with a Parkinson's Disease Sleep Scale-2 (PDSS-2) total score ≥18, and were treated with 3–8 daily intakes L-dopa/DDCI for at least 4 weeks
- Patients were excluded from the study if they had severe or unpredictable OFF periods or if they had major non-PD related sleep disorders
- The primary endpoint was change from baseline to Week 6 in PDSS-2
- Secondary endpoints included functional motor and non-motor assessments (Movement Disorder Society [MDS]-Unified Parkinson's Disease Rating Scale [UPDRS], MDS-Non-motor Scale [NMS], 8-item PD Questionnaire [PDQ-8], 16-item PD Fatigue Scale [PFS-16], ON/OFF home diary), and Clinical and Patient Global Impression of Change (CGI-C and PGI-C) (**Figure 1**)
- Safety and tolerability were evaluated throughout the study by assessing treatment-emergent adverse events (TEAEs)

**Figure 1.** OASIS study design and endpoints



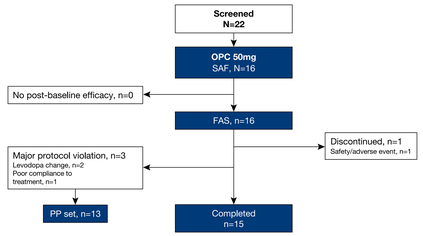

*0–5 days prior V2b / if the patients completed the diary satisfactory, it should be immediately continued with V2b, at the same day.
**Objective measurement of motor symptoms (AX3 device).
CGI-C, Clinical Global Impression of Change; DDCI, dopa decarboxylase inhibitor; EDV, early discontinuation visit; EMD, early morning dystonia; L-dopa, levodopa; MDS-NMS, Movement Disorder Society Non-Motor Scale; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDSS-2, PD Sleep Scale-2; PDQ-8, 8-item PD Questionnaire; PFS-16, 16-item PD Fatigue Scale; PGI-C, Patient Global Impression of Change; PSV, post-study visit; V, visit.

## Results

### Patient population

- Of the 22 screened patients, 16 received OPC 50 mg and were included in the safety set (all patients who took ≥1 dose of OPC) and in the full analysis set (all patients allocated to treatment with ≥1 key efficacy assessment) (**Figure 2**)
- At baseline, the mean duration of PD was 6.0 years, the mean duration of motor fluctuations was 1.5 years and the mean PDSS-2 score was 26.9 (**Table 1**)

**Figure 2.** Patient disposition




FAS, full analysis set; OPC, opicapone; SAF, safety analysis set

**Table 1.** Baseline and disease characteristics

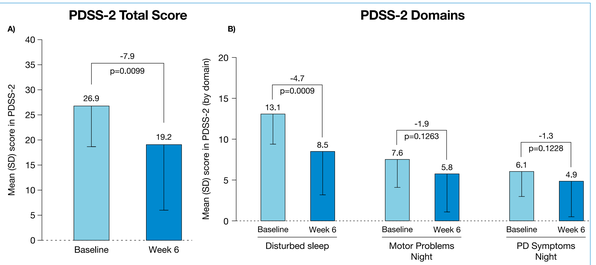
| | Opicapone 50 mg (safety set) N=16 |
|---|---|
| **Demographic characteristics** | |
| Age (years), mean (SD) | 65.4 (9.4) |
| Gender (male), n (%) | 8 (50.0) |
| Caucasian, n (%) | 16 (100.0) |
| Weight (kg), mean (SD) | 72.8 (14.8) |
| BMI (kg/m²), mean (SD) | 27.2 (4.5) |
| **Clinical characteristics** | |
| PD duration (years), mean (SD) | 6.0 (2.2) |
| MF duration (years), mean (SD) | 1.5 (0.8) |
| PD sleep disorder duration (years), mean (SD) | 3.2 (2.5) |
| Hoehn & Yahr<br>Stage 2, n (%)<br>Stage 3, n (%) | <br>13 (81.3)<br>3 (18.8) |
| PDSS-2 score,* mean (SD) | 26.9 (8.2) |
| PFS-16 score,* mean (SD) | 59.8 (8.7) |
| OFF time (h),* mean (SD) | 6.1 (1.7) |
| MDS-UPDRS Part III (motor examination) score,* mean (SD) | 31.3 (14.4) |
| **PD medication** | |
| Levodopa amount (mg),* mean (SD) | 536.7 (202.1) |
| Levodopa number of intakes per day, n (%)<br>3 intakes<br>4 intakes<br>5 intakes<br>6 intakes | <br>1 (6.3)<br>6 (37.5)<br>8 (50.0)<br>1 (6.3) |
| Levodopa/benserazide, n (%) | 11 (68.8) |
| Levodopa/carbidopa, n (%) | 9 (56.3) |

*In the full analysis set, defined as all patients allocated to treatment with ≥1 key efficacy assessment (same population as safety set, defined as all patients who took ≥1 dose of OPC).
BMI, body mass index; FAS, Full Analysis Set; MDS-UPDRS, Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; MF, motor fluctuations; OPC, opicapone; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PFS, Parkinson's Disease Fatigue Scale; PP, per protocol; SAF, Safety Analysis Set; SD, standard deviation

### Efficacy endpoints

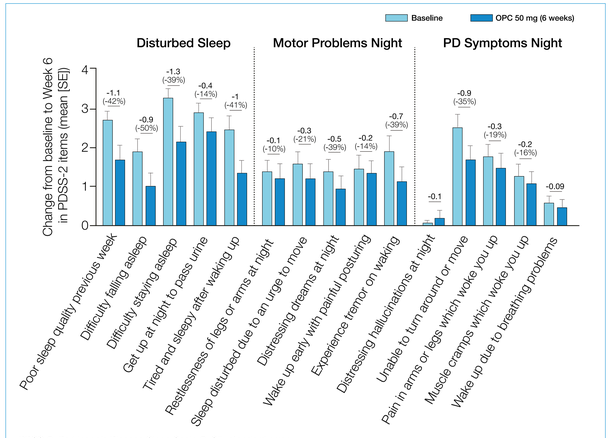
- At Week 6, there was a significant reduction of -7.9 points (p=0.0099) in total PDSS-2 score (**Figure 3A**)
  - Minimal clinically important difference for the PDSS-2 score is -3.44 points[8]
- There was also a significant mean change of -4.7 in the PDSS-2 domain of disturbed sleep (p=0.0009) (**Figure 3B**)
- Patients experienced reductions in the scores for poor sleep quality in the previous week (-1.1 [0.3]; -42%), sleep latency (-0.9 [0.4]; -50%), sleep fragmentation (-1.3 [0.4]; -39%), and restorative sleep (-1 [0.3]; -41%), less difficulty moving or turning in bed (-0.9 [0.3]; -35%) and less tremor upon waking (-0.7 [0.3], -39%) (**Figure 4**)

**Figure 3.** Change from baseline to Week 6 in PDSS-2 total score and in PDSS-2 domains (full analysis set)




PD, Parkinson's disease; PDSS-2, PD Sleep Scale-2; SD, standard deviation

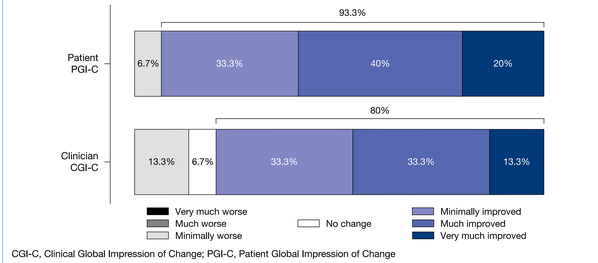
**Figure 4.** Change from baseline to Week 6 in PDSS-2 subitems by domain (full analysis set).




PDSS-2, Parkinson's Disease Sleep Scale-2; SE, standard error.

- Fatigue on PFS-16 was significantly improved from baseline to Week 6, with a mean reduction of -9.6 (95% confidence interval [CI] -17.5,-1.7; p=0.0211)
- The mean change from baseline to Week 6 in MDS-NMS total score of -28.9 (95% CI -44.7,-13.2; p=0.0052), demonstrated a significant reduction in the non-motor symptoms of PD
- At Week 6 there were also reductions in the scores of MDS-UPDRS Part III (-6.3 [95% CI -11.6,-0.9; p=0.0253] and Part IV (-1.2 [95% CI -2.0,-0.4; p=0.0044], respectively)
- Significant improvements in the quality of life were also reported as suggested by a reduction of -14.2 (95% CI -23.3,-5.0; p=0.0051) in the PDQ-8 score
- Absolute OFF time was reduced (-142.1 min), while ON time without dyskinesia was increased (+127.1 min)
- Most patients (93.3%) and most clinicians (80.0%) reported an improvement as evaluated by the PGI-C and CGI-C, respectively (**Figure 5**)

**Figure 5.** PGI-C and CGI-C at Week 6 (full analysis set)




CGI-C, Clinical Global Impression of Change; PGI-C, Patient Global Impression of Change

### Safety endpoint

- OPC was generally well tolerated: 11 patients (68.8%) experienced TEAEs, and only one patient (6.3%) discontinued due to TEAEs (**Table 2**)

**Table 2.** Safety summary

| Summary of TEAEs | OPC 50 mg (safety set) N=16 |
|---|---|
| Any TEAE, n (%) | 11 (68.8) |
| Any serious TEAE, n | 0 |
| Any treatment-related TEAE, n (%) | 4 (25.0) |
| Type of treatment-related[a] TEAEs[b], n (%)<br>Somnolence<br>Tremor<br>Dry mouth<br>Muscle spasm<br>Hypotension | <br>1 (6.3)<br>1 (6.3)<br>1 (6.3)<br>1 (6.3)<br>1 (6.3) |
| Any serious treatment-related TEAE, n | 0 |
| Any TEAE leading to death, n | 0 |
| Any TEAE leading to dose interruption, n (%) | 1 (6.3) |
| Any TEAE leading to discontinuation, n (%) | 1 (6.3) |

Safety set defined as all patients who took at least one dose of opicapone; [a]At least possibly related TEAEs; [b]Patients could experience more than one TEAE.
OPC, opicapone; TEAE, treatment-emergent adverse event.

## CONCLUSION

Adding OPC 50 mg to L-dopa therapy improved sleep disturbances and other non-motor symptoms, supporting OPC's potential to treat motor fluctuations in patients with PD-related sleep disorders

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### Conflict of interests

Miguel Gago has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Bial, and Zambon. Raquel Costa, Miguel Fonseca, Joana Almeida, Helena Brigas, José-Francisco Rocha, and Joerg Holenz have received personal compensation for serving as employees of Bial. Ghazal Banisadr has received personal compensation for serving as an employee of Amneal Pharmaceuticals. Joerg Holenz has received personal compensation for serving as an officer or member of the Board of Directors for Bial Biotech, Bial RD Investments, and Bial Portela SA. Joerg Holenz has received personal compensation serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Wiley. Joerg Holenz has stock in Astra Zeneca. Joerg Holenz has received intellectual property interests from a discovery or technology relating to health care. The institution of Joaquim Ferreira has received personal compensation for serving as a Consultant for Abbvie, Bial, Biogen, Lundbeck, and Neurocrine. The institution of Joaquim Ferreira has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Abbvie, Bial, Biogen, Lundbeck, and Neurocrine. The institution of Joaquim Ferreira has received personal compensation for serving on a Speakers Bureau for Abbvie, BIAL, Infucare, Nordic, ONO, and SK Chemicals.

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