Opicapone for the Treatment of Early Wearing-Off in Levodopa-Treated Parkinson's Disease Patients

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Background

- Levodopa (L-dopa) is the most effective therapy for the symptomatic treatment of Parkinson's disease (PD); however, its therapeutic effect decreases with the progression of PD, leading to wearing-off symptoms[1,2]
- Strategies to manage wearing-off symptoms include increasing the total dose of L-dopa/dopa decarboxylase inhibitor (DDCI), dividing the total daily dose into smaller, more frequent doses, or adding a catechol-O-methyl transferase (COMT) inhibitor[3,4]
- Opicapone (OPC) is a third-generation, once-daily COMT inhibitor used to optimise L-dopa therapy[5]
- OPC is generally well tolerated and effective in reducing OFF time in two large clinical trials (BIPARK I and II) when given as add-on to L-dopa/DDCI therapy[5,6]

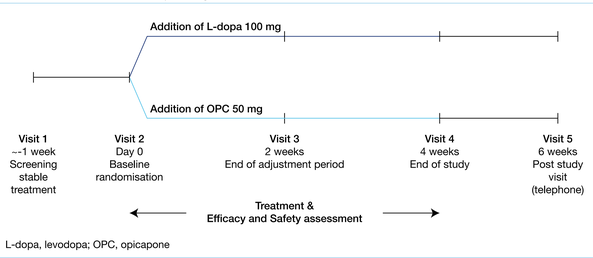
Objective

The Korean and European eArly levoDopa with Opicapone in Parkinson's paTients wIth motOr fluctuatioNs (ADOPTION) studies aimed to explore the efficacy of OPC 50 mg versus an additional 100 mg L-dopa dose to treat early wearing-off in patients with PD

Methods

- The ADOPTION study programme included two similarly designed open-label, phase 4 studies conducted in South Korea and Europe
- Patients with PD who experienced early wearing-off symptoms were randomised to receive OPC 50 mg or an additional L-dopa dose of 100 mg as add-on to their current L-dopa/DDCI therapy for 4 weeks (**Figure 1**)
  - Patients were included if they were aged ≥30 years with idiopathic PD and a modified Hoehn and Yahr stage of 1-3 (at ON state) treated with a stable regimen of L-dopa/DDCI (max 600 mg; 3-4 daily intakes, for ≥4 weeks) with signs of wearing-off (average of total daily OFF time ≥1 hour) for ≥4 weeks but <2 years
  - Patients were excluded in case of severe and/or unpredictable OFF periods or an average total daily OFF time >5 hours while awake
- In this integrated analysis, patient-level data from both studies were pooled
- The primary endpoint was change from baseline in absolute OFF time
- Secondary endpoints included Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS), 8-item PD Questionnaire (PDQ-8), Clinical Global Impression of Improvement (CGI-I), and Patient Global Impression of Improvement (PGI-I)

Figure 1. ADOPTION study design



L-dopa, levodopa; OPC, opicapone

Results

Patient population

- In total, 244 patients were randomised to either OPC 50 mg (n=126) or L-dopa 100 mg (n=118)
  - The full analysis set included 120 patients (OPC 50 mg) and 117 patients (L-dopa 100 mg)
- Baseline characteristics were generally similar between the two groups (**Table 1**)

Efficacy

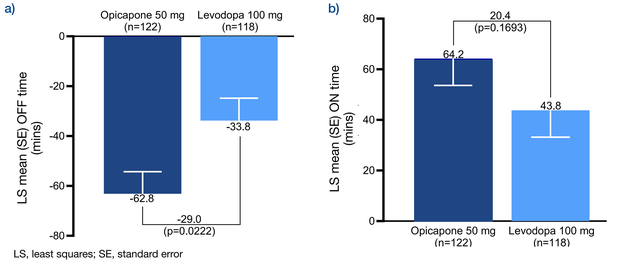
Table 1. Demographic and baseline characteristics

	Opicapone 50 mg n=126	Levodopa 100 mg n=118	Total N=244
Mean age, year (SD)	64.1 (8.3)	64.6 (9.1)	64.3 (8.7)
Male, n (%)	65 (51.6)	63 (52.9)	128 (52.8)
Mean height, cm (SD)	164.0 (10.0)	163.5 (9.6)	163.8 (9.8)
Mean weight, kg (SD)	67.8 (14.4)	66.9 (13.0)	67.4 (13.7)
Mean H&Y, stage (SD)	2.0 (0.5)	2.1 (0.5)	2.0 (0.5)
Mean PD duration, year (SD)	5.1 (3.6)	5.3 (3.6)	5.2 (3.6)
Mean MDS-UPDRS motor score (SD)	23.7 (10.8)	24.7 (11.5)	24.2 (11.1)
Mean PDQ-8, SI (SD)	17.4 (13.2)	18.4 (14.6)	17.9 (13.9)
Mean daily OFF time, hours (SD)	3.4 (1.0)	3.4 (1.0)	3.4 (1.0)
Mean total ON time, hours (SD)	12.8 (1.6)	12.8 (1.6)	12.8 (1.6)
Mean ON time without dyskinesia, hours (SD)	11.6 (2.6)	11.2 (3.3)	11.4 (3.0)
Mean levodopa amount at baseline, mg (SD)	398.3 (117.4)	412.4 (119.5)	405.2 (118.7)
Patients receiving 3 or 4 levodopa intakes per day, n (%)*	101 (80.2)	93 (78.2)	194 (79.5)
3 intakes	24 (19.0)	25 (21.0)	49 (20.1)
4 intakes			
Patients receiving MAO-Bi and/or DA, n (%)	106 (84.1)	99 (83.9)	205 (84.0)
DA	77 (61.1)	75 (63.6)	152 (62.3)
Pramipexole	56 (44.4)	53 (44.9)	109 (44.7)
Rotigotine	5 (4.0)	5 (4.2)	10 (4.1)
Ropinirole	22 (17.5)	19 (16.1)	41 (16.8)
MAO-Bi	67 (53.2)	67 (56.8)	134 (54.9)
Rasagiline	59 (46.8)	51 (43.2)	110 (45.1)
Safinamide	7 (5.6)	13 (11.0)	20 (8.2)
Selegiline	2 (1.6)	3 (2.5)	5 (2.0)

*One patient took 5 intakes in the opicapone 50 mg group
DA, dopamine agonists; H&Y, Hoehn and Yahr; LEDD, levodopa equivalent daily dose; MAO-Bi, monoamine oxidase-B inhibitors; MDS-UDPRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDQ-8, 8-item PD questionnaire; SD, standard deviation; SI, summary index

- At Week 4, mean (standard error [SE]) change from baseline in absolute OFF time was -62.8 min (8.8) for OPC 50 mg and -33.8 min (9.0) for L-dopa 100 mg, resulting in a significant difference of -29.0 min (p=0.0222) (**Figure 2a**)
- OPC 50 mg provided a correspondingly greater increase than treatment with L-dopa 100 mg in total ON time (64.2 min vs 43.8 min; p=0.17) (**Figure 2b**), most of which was without any dyskinesia
- A daytime reduction in OFF time was consistently observed at all hours in the OPC 50 mg group. The addition of L-dopa 100 mg did not result in a daytime reduction in OFF time at all hours (**Figure 3**)
- The change from baseline in MDS-UPDRS Part III (motor) scores (during ON) was significantly greater for the OPC 50 mg group than the L-dopa 100 mg group (-4.1 vs -2.5, respectively; p=0.04) (**Table 2**)
- Overall, both groups showed improvements in MDS-UPDRS Part IV and PDQ-8 scores (**Table 2**)
- OPC-treated patients showed greater improvements on the CGI-I (84.2%) and PGI-I (79.7%) scales compared with the L-dopa 100 mg group (72.4% and 69.0%, respectively) (**Table 2**)

Figure 2. Change from baseline to Week 4 in absolute a) OFF time and b) ON time (full analysis set)



LS, least squares; SE, standard error

Figure 3. Relative change from baseline in daytime OFF-fluctuation a) OPC 50 mg, and b) L-dopa 100 mg (full analysis set)

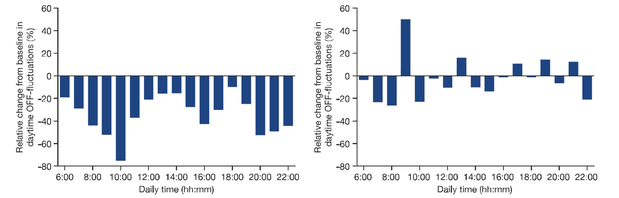


Table 2. Summary of secondary efficacy endpoint (full analysis set)

	Opicapone 50 mg (n=120)	Levodopa 100 mg (n=117)
MDS-UPDRS scores		
Part III		
LS mean (SE) change from baseline	-4.1 (0.6)	-2.5 (0.6)
LS mean difference vs levodopa 100 mg (95% CI)	-1.7 (-3.3, -0.4)	
p-value for opicapone 50 mg vs levodopa 100 mg	p=0.0445	
Part IV		
LS mean (SE) change from baseline	-1.1 (0.2)	-0.8 (0.2)
LS mean difference vs levodopa 100 mg (95% CI)	-0.3 (-0.7, 0.1)	
p-value for opicapone 50 mg vs levodopa 100 mg	p=0.1734	
PDQ-8, SI		
LS mean (SE) change from baseline	-2.7 (1.0)	-1.9 (1.0)
LS mean difference vs levodopa 100 mg (95% CI)	-.09 (-3.6, 1.9)	
p-value for opicapone 50 mg vs levodopa 100 mg	p=0.5447	
CGI-I		
Participants with improvements,[a] n/N (%)	96/112 (84.2)	84/116 (72.4)
PGI-I		
Participants with improvements,[a] n/N (%)	90/113 (79.7)	80/116 (69.0)

Full analysis set, defined all randomly assigned patients who took at least one dose of study drug and had at least one efficacy assessment after baseline.
[a]Includes any improvement (minimal, much and very much).
CGI-I, Clinical Global Impression of Improvement; CI, confidence interval; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-8, 8-item PD Questionnaire; PGI-I, Patient Global Impression of Improvement; SE, standard error, SI, summary index.

Safety

- OPC was generally well tolerated: 47 patients (37.6%) reported AEs in the OPC 50 mg group compared with 29 (24.6%) in the L-dopa 100 mg group
- A total of 6 patients discontinued due to AEs (4 [3.2%] in the OPC group and 2 [1.7%] in the L-dopa 100 mg group)

CONCLUSION

- In this integrated analysis, adding OPC was superior to increasing the daily L-dopa dose in reducing wearing-off symptoms in patients with PD
  - OPC showed improvements in motor function and quality of life
  - OPC improved the general health status of the patients
- Better and sustained improvements in OFF time were reported with OPC 50 mg during the 24-hour period when compared to an additional dose of L-dopa (two 50 mg intakes)
- OPC is a well-tolerated and effective option for patients who have developed the early signs of wearing-off

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Conflict of interests

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. JYL has received personal compensation for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Parkinsonism & Related Disorders. JYL has received research support from National Research Foundation funded by Ministry of Science and ICT, South Korea. JYL has received research support from SMG-SNU Boramae Medical Center multidisciplinary research grant-in-aid. HM has nothing to disclose. BJ has received personal compensation for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Elsevier. 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