OPICAPONE AS FIRST STRATEGY FOR THE TREATMENT OF WEARING-OFF IN KOREAN PATIENTS WITH PARKINSON'S DISEASE

Jee-Young Lee[1], Joaquim J. Ferreira[2], Hyeo-il Ma[3], José-Francisco Rocha[4], Beomseok Jeon[5], on behalf of Korean OGT_001 study investigators

[1]Department of Neurology, SMG-SNU Boramae Medical Center, Seoul, South Korea; [2]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; [3]Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, South Korea; [4]BIAL–Portela & Ca S.A, Coronado, Portugal; [5]Department of Neurology, Seoul National University Hospital, Seoul, South Korea

Introduction

Common therapeutic strategies to manage early wearing-off symptoms include increasing the total daily dose of L-dopa/DDCI and/or fractioning the total dose in smaller, more frequent doses. However, clinical experience suggests that these conventional strategies are short-term solutions and are associated with an increased risk of dyskinesia and/or suboptimal exposure for patients and might therefore not represent the optimal approach to treat wearing-off. Furthermore, these strategies do not address the pulsatile nature and short half-life of L-dopa.

An alternative pharmacological approach is to optimize L-dopa delivery by administering L-dopa/DDCI with catechol-O-methyltransferase (COMT) inhibitors that increase the plasma half-life of L-dopa, thus extending the duration of its clinical effect.

Objective

To explore the efficacy of opicapone (OPC)-50mg or an extra dose of levodopa (L-DOPA)-100mg to treat wearing-off in patients with Parkinson's disease (PD).

Methods

ADOPTION was a randomized, parallel-group, open-label, Phase 4 study conducted in Korea. At baseline, eligible patients were randomized (1:1) to opicapone 50 mg (n=87) or L-dopa 100 mg (n=81) (added to current L-dopa/DDCI therapy) for 4 weeks. The main efficacy endpoint was change from baseline to end of study in absolute off time. Other endpoints included changes in on time, in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and 8-item PD Questionnaire (PDQ-8) scores, and the Clinical and Patient Global Impression of Improvement/Change (CGI-I, PGI-C).

Results

Figure 1: Study Design

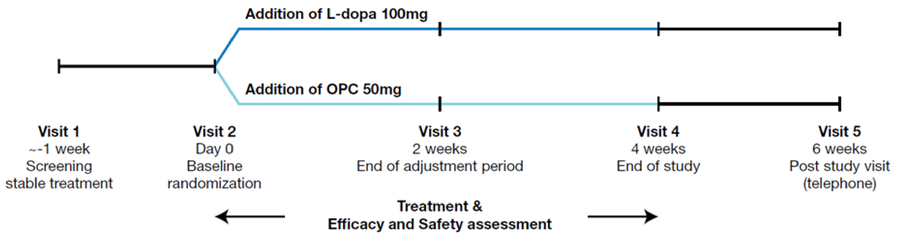

Table 1: Baseline characteristics

	Opicapone 50 mg N=88	L-dopa 100 mg N=81
Mean age, year (SD)	64.1 (7.5)	64.2 (8.0)
Male, n (%)	39 (44.3)	44 (54.3)
Mean weight, kg (SD)	62.8 (10.1)	63.7 (10.7)
Mean H&Y, stage (SD)	2.0 (0.5)	2.1 (0.6)
Mean PD duration, year (SD)	5.0 (3.5)	5.7 (3.8)
Mean MDS-UPDRS, score (SD)		
Part I	6.4 (4.0)	7.3 (4.5)
Part II	6.6 (4.7)	8.1 (5.9)
Part III	22.0 (10.0)	23.7 (11.5)
Part IV	4.0 (1.7)	4.2 (1.9)
Total	39.0 (14.5)	43.3 (18.9)
Mean PDQ-8, score (SD)	5.3 (4.3)	5.6 (4.7)
Mean daily *off* time, hours (SD)	3.4 (1.1)	3.4 (1.0)
Mean total *on* time, hours (SD)	13.0 (1.7)	13.0 (1.5)
Mean L-dopa amount, mg (SD)	402.7 (127.7)	414.4 (120.3)
Patients receiving MAO-Bi and/or DA, n (%)	74 (84.1)	70 (86.4)
DA	55 (65.5)	60 (74.1)
Pramipexole	43 (58.1)	47 (67.1)
Ropinirole	18 (24.3)	15 (21.4)
MAO-Bi	47 (56.0)	42 (51.9)
Rasagiline	46 (62.2)	38 (54.3)
Selegiline	1 (1.4)	3 (4.3)
Safinamide	1 (1.4)	1 (1.4)

Table 2: Efficacy Outcomes

	Opicapone 50 mg N=84	L-dopa 100 mg N=81
OFF-time (min)		
Adjusted mean ± SE change from baseline	-62.1 ± 9.8	-16.7 ± 10.0
Mean difference vs. L-dopa 100 mg (95%CI)	-45.4 (-73.1, -7.6)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	**0.0015**	
OFF-time responder rate (reduction of ≥1 hour); n (%)	44 (52.4)	35 (43.2)
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.2384	
Total ON-time (min)		
Adjusted mean ± SE change from baseline	70.2 ± 11.3	35.6 ± 11.5
Mean difference vs. L-dopa 100 mg (95%CI)	34.5 (2.7, 66.4)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	**0.0338**	
ON-time without dyskinesia (min)		
Adjusted mean ± SE change from baseline	64.8 ± 13.4	56.6 ± 13.6
Mean difference vs. L-dopa 100 mg (95%CI)	8.2 (-29.5, 45.9)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.6679	
ON-time with troublesome dyskinesia (min)		
Adjusted mean ± SE change from baseline	-5.8 ± 8.6	-2.3 ± 8.7
Mean difference vs. L-dopa 100 mg (95%CI)	-3.5 (-27.7, 20.6)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.7721	
MDS-UPDRS scores		
Part III		
Adjusted mean ± SE change from baseline	-3.4 ± 0.7	-2.5 ± 0.7
Mean difference vs. L-dopa 100 mg (95%CI)	-0.9 (-2.9, 1.1)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.3591	
Part IV		
Adjusted mean ± SE change from baseline	-0.8 ± 0.2	-0.6 ± 0.2
Mean difference vs. L-dopa 100 mg (95%CI)	-0.2 (-0.7, 0.3)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.3702	
PDQ-8 scores		
Adjusted mean ± SE change from baseline	-2.6 ± 1.3	-1.1 ± 1.2
Mean difference vs. L-dopa 100 mg (95%CI)	-1.6 (-5.1, 1.9)	
p-value for opicapone 50 mg vs. L-dopa 100 mg	0.3620	
CGI-I		
Participants with improvement, n (%)	62 (80.5%)	54 (67.5%)
PGI-C		
Participants with improvement, n (%)	59 (77.6%)	48 (60.0%)

CONCLUSIONS

- Opicapone 50 mg was more effective than an additional L-dopa dose of 100 mg to treat early wearing-off in patients with PD

Figure 1: Adjusted mean (SE) change from baseline to end of study treatment in absolute off time (A), absolute on time (B) and absolute on time without dyskinesia (C) in the full analysis set. L-dopa, levodopa; SE standard error

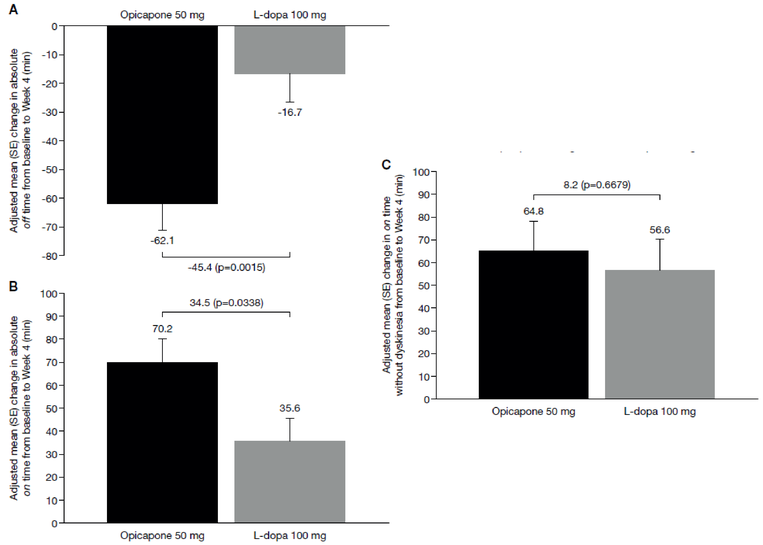

Table 3: Safety

	Opicapone 50 mg N=88	L-dopa 100 mg N=81
Any AE, n (%) *	33 (37.9)	15 (18.5)
Dizziness	8 (9.2)	3 (3.7)
Dyskinesia	7 (8.1)	1 (1.2)
Constipation	4 (4.6)	2 (2.5)
Headache	3 (3.5)	-
Asthenia	3 (3.5)	2 (2.5)
Severity, n (%)		
Mild	28 (32.2)	12 (14.8)
Moderate	6 (6.9)	3 (3.7)
Severe	1 (1.2)	-
Serious AEs, n (%)	3 (3.5)	1 (1.2)
Spinal compression fracture	2 (2.3)	-
Subdural hematoma	1 (1.2)	-
Upper limb fracture	-	1 (1.2)
AEs leading to discontinuation, n (%)	3 (3.5)	2 (2.5)
Spinal compression fracture	1 (1.2)	-
Upper limb fracture	-	1 (1.2)
Dizziness	1 (1.2)	-
Insomnia	-	1 (1.2)
Rash	1 (1.2)	-
Any drug-related AE, n (%) *	22 (25.3)	10 (12.4)
Dyskinesia	6 (6.9)	1 (1.2)
Dizziness	5 (5.8)	2 (2.5)
Constipation	4 (4.6)	2 (2.5)
Headache	3 (3.5)	-
Serious drug-related AE, n (%)	1 (1.2)	-
Subdural hematoma	1 (1.2)	-