Evaluation of opicapone's efficacy in Parkinson's disease patients with motor fluctuations: phase III, randomized, double-blind, placebo- and active-controlled study (BIPARK I)

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Introduction

Levodopa still remains the most effective symptomatic treatment for Parkinson's Disease (PD). However, following oral administration, levodopa is extensively metabolized in the periphery by dopa decarboxylase and catechol-O-methyltransferase (COMT). Opicapone (OPC) is a novel 3rd generation COMT inhibitor developed to fulfil the need for a more potent, safer and longer acting COMT inhibitor [1,2].

Objective

To investigate the efficacy and safety of 3 different doses of OPC (5, 25 and 50 mg) administered once daily, compared with entacapone (ENT) and placebo, in patients with PD and motor fluctuations.

Methods

Population

BIPARK I was a multinational (Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Montenegro, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain and Ukraine), multicentre (130 sites), double-blind (DB), placebo- and active-controlled, parallel-group study. Eligible patients were male or female, aged 30-83 years, with a 3-year diagnosis of idiopathic PD, Hoehn and Yahr 1-3 at ON-state, receiving treatment with levodopa for at least 1 year, experiencing end-of-dose motor fluctuations with ≥ 1.5 hours of OFF-time per day (not including pre-dose morning akinesia) and able to keep accurate 24h diaries.

Study Design

Subjects were randomly assigned at baseline to OPC (5, 25 and 50 mg once-daily), ENT (200 mg with every levodopa dose) or Placebo (1:1:1:1:1 ratio). The study medication was administered in combination with existing levodopa therapy. During first 3 weeks of treatment, the Investigator could adjust the levodopa dose according to subject response, not exceeding baseline level. Other background PD drugs were to be stable throughout the study (Figure 1). The primary efficacy variable was the mean change from baseline to endpoint in absolute OFF-time, as measured by 24h Hauser diaries over 3 days preceding each timepoint. Secondary variables included proportion of OFF- and ON-time responders (≥ 1h improvement), Investigators' and Subjects' Global Assessment of Change (IGAC & SGAC), UPDRS, quality of life (PDQ-39), NMSS, PDSS and safety assessments (including mMIDI, C-SSRS and laboratory tests).

Statistical Analyses

Primary efficacy analyses: multiple one-sided tests based on analysis of covariance (ANCOVA) were used to determine superiority vs. placebo (Full Analysis Set) and non-inferiority vs. ENT (Per Protocol Set) in a sequential gatekeeping procedure to control for multiplicity. The family-wise error rate was 0.025 (corresponding to 0.05 for 2-sided tests). For each OPC dose, non-inferiority vs. ENT was tested only if the efficacy of OPC vs. placebo had been established. The pre-specified non-inferiority margin was 30 minutes. The ANCOVA model included treatment group and region as fixed effects and baseline value as a covariate. *Secondary efficacy analyses:* continuous variables were analyzed with an ANCOVA model similar to that used for the primary variable. The responder rates were compared with a Cochran–Mantel–Haenszel (CMH) test stratified by region.

Results

Patient Disposition, Baseline Characteristics

- The Full Analysis Set (FAS) comprised a total of 590 patients: placebo n=120, ENT n=120, OPC 5 mg n=119, OPC 25 mg n=116, OPC 50 mg n=115.
- Baseline characteristics were comparable across treatment groups (Table 1).

Figure 1: Study Design

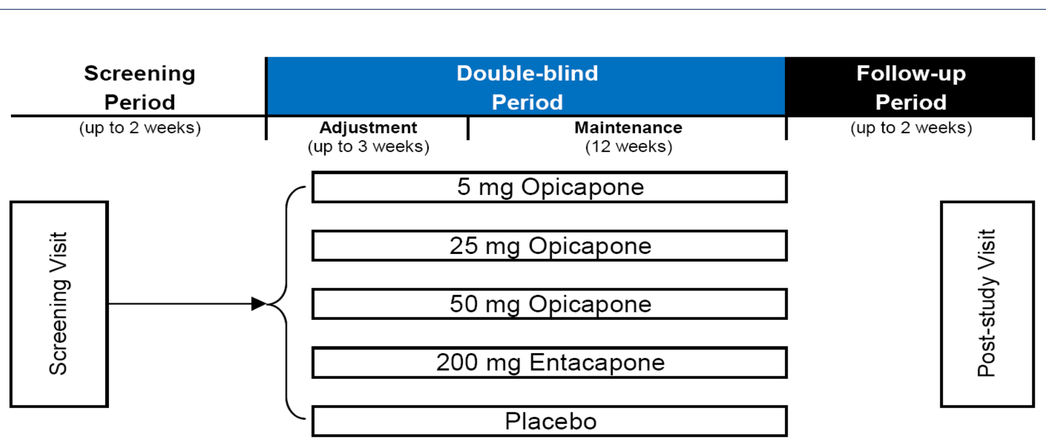


Table 1: Demographics and Baseline Characteristics

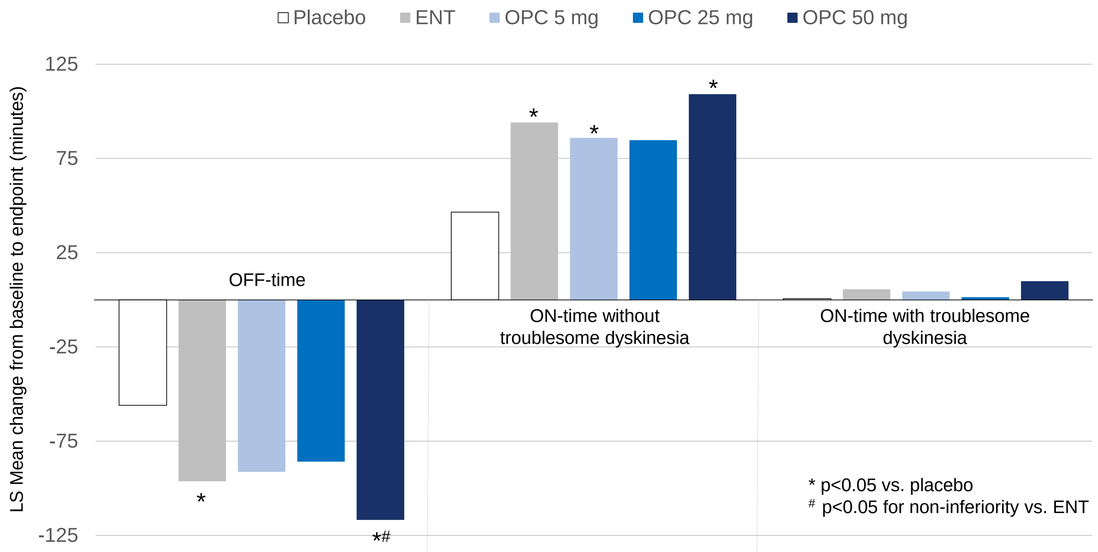
Characteristics	Placebo n=120	ENT n=120	OPC 5 mg n=119	OPC 25 mg n=116	OPC 50 mg n=115
Gender, male, n (%)	70 (58.3%)	74 (61.7%)	68 (57.1%)	65 (56.0%)	69 (60.0%)
Age mean (SD), years	64.5 (9.2)	63.6 (8.8)	63.3 (9.2)	64.3 (9.0)	63.5 (9.2)
Race, n (%)					
White	120 (100%)	120 (100%)	119 (100%)	116 (100%)	115 (100%)
Disease duration, years, mean (SD)	7.7 (4.2)	7.1 (4.1)	7.5 (3.6)	7.2 (4.1)	7.0 (3.8)
Daily OFF-time, hours, mean (SD)	6.2 (1. 8)	6.5 (2.2)	6.7 (2.1)	6.9 (2.2)	6.2 (1.8)
Daily ON-time with troublesome dyskinesia, hours, mean (SD)	0.4 (1.1)	0.3 (0.9)	0.4 (1.18)	0.3 (0.8)	0.3 (1.0)
UPDRS III (ON), mean (SD)	27.6 (11.7)	25.8 (13.8)	28.5 (11.9)	29.0 (12.9)	28.4 (13.7)
H&Y stage (ON), mean (SD)	2.4 (0.5)	2.3 (0.55)	2.4 (0.4)	2.4 (0.5)	2.4 (0.5)
Daily levodopa, mg, mean (SD)	675 (302.1)	645 (329.7)	642 (310.3)	654 (324.3)	695 (337.5)

Full Analysis Set; UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr; PD: Parkinson's Disease; Scale; SD: standard deviation

Efficacy

- OPC 50 mg and ENT significantly reduced the daily OFF-time and increased the ON-time without troublesome dyskinesia. The non-inferiority endpoint was met for the OPC 50 mg group (Figure 2).
- OPC 50 mg achieved statistical significance for both OFF- and ON-time responders rates vs. placebo, while ENT did not (Figure 3).
- Treatment with OPC was associated with favorable ratings in IGAC & SGAC, in contrast to essentially no difference between ENT and Placebo in either assessments.
- No significant differences between treatment groups were observed for UPDRS, PDQ-39, NMSS or PDSS.

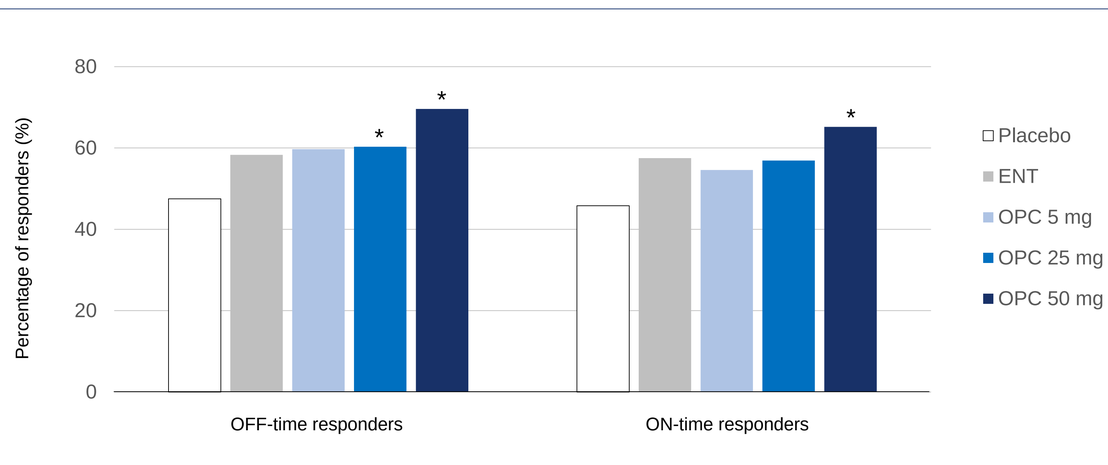
Figure 2: Primary Absolute OFF- and ON-time Endpoint Analyses



LS Mean Differences			
OPC 50 mg vs. placebo	-60.8 p=0.0015	62.6 p=0.0016	9.3 p=0.2635
OPC 25 mg vs. placebo	-29,9 p=0.0796	38.2 p=0.0535	0.8 p=0.9219
OPC 5 mg vs. placebo	-35.2 p=0.0058	39.4 p=0.0442	3.8 p=0.6436
Entacapone vs. placebo	-40.3 p=0.0141	47.6 p=0.0150	5.0 p=0.5436
OPC 50 mg vs. ENT (NI)	-26.2 p=0.00518	-	-

NI: non-inferiority; ON-time without troublesome dyskinesia = ON-time without dyskinesia + ON-time with non-troublesome dyskinesia.
OFF-time comparisons as per the gatekeeping procedure. OPC 5 mg and 25 mg non-inferiority hypotheses were not tested as superiority vs. placebo was not achieved.

Figure 3: Key Secondary – Responder Rates



Responders: ≥ 1 hour improvement; ON-time: total ON-time; * p<0.05

Safety

- Treatment-emergent adverse events (TEAEs) were reported for 49.6% subjects in placebo, 51.6% to 54.6% in OPC and 56.6% in ENT.
- Compared to placebo, the most commonly reported TEAEs with OPC were dyskinesia (12.4% vs. 4.1%), insomnia (4.5% vs. 0.8%), and dizziness (3.1% vs. 0.8%).
- Compared to ENT, the profile of TEAEs was similar. Nausea was more common in ENT (6.6% vs. 2.2%) while dyskinesia was more common in OPC (12.4% vs. 8.2%).
- Diarrhoea led to discontinuation of 1.6% patients in ENT compared to no cases in OPC.

CONCLUSION

- Treatment with OPC 50 mg significantly reduced the daily OFF-time and increased the ON-time without troublesome dyskinesia.
- The placebo-adjusted OFF-time reduction in the OPC 50 mg group (-60.8 min) was 51% higher than the observed effect for ENT (-40.3 min).
- OPC 50 mg once-daily was effective in the treatment of motor fluctuations with a favourable profile compared to ENT.

References

1-Kiss LE, et al. J Med Chem, 53:3396-3411, 2010. 2-Almeida L., et al. Clin Pharmacokinet, 52:139–151, 2013.

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