Pooled efficacy analysis of opicapone as adjunctive therapy to levodopa in patients with Parkinson’s disease and motor fluctuations

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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 evaluate the efficacy profile of OPC based on pooled efficacy data from two pivotal, multinational, double-blind, randomized, parallel-group, 14- to 15-week, placebo- and active-controlled studies in patients with PD and motor fluctuations (BIPARK I and II) [3,4].

Methods
Patient-level data of matching treatment arms from BIPARK I and II studies was combined (placebo, OPC 25 mg and OPC 50 mg). The studies had similar designs, eligibility criteria and assessment methods. 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 and experiencing end-of-dose motor fluctuations with ≥ 1.5 hours of OFF-time per day (not including pre-dose morning akinesia). The primary efficacy variable in both studies was the change from baseline in absolute OFF-time based on patient’s diaries. The same variable was used for the primary analysis of the pooled data, assessed by an ANCOVA with study and geographical area as factors and baseline as covariate. OFF- and ON-time responder rates were analysed by a Cochran-Mantel-Haenszel test stratified by study. The Investigator’s and Subject’s Global Assessment of Change (IGAC & SGAC) were analysed by a van Elteren’s test. All p-values are exploratory.

Results
Patient Disposition, Baseline Characteristics and Concomitant PD Medication
- The Full-Analysis Set comprised a total of 758 patients (placebo n=255, OPC 25 mg n=241, OPC 50 mg n=262).
- Demographic and baseline characteristics were comparable across treatment groups (Table 1).
- Completion rate was high across all groups: 90.7%, 91% and 87.5% for placebo, OPC 25 mg and OPC 50 mg, respectively.

Figure 1: Subject Disposition

Table 1: Baseline Patient Characteristics and Concomitant PD Medication

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo n=257</th>
<th>OPC 25 mg n=241</th>
<th>OPC 50 mg n=262</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male, n (%)</td>
<td>142 (55.3%)</td>
<td>149 (61.7%)</td>
<td>160 (60.4%)</td>
</tr>
<tr>
<td>Age mean (SD), years</td>
<td>62.8 (9.1)</td>
<td>62.4 (8.8)</td>
<td>64.5 (8.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>211 (82.1%)</td>
<td>209 (86.5%)</td>
</tr>
<tr>
<td>Disease duration, years, mean (SD)</td>
<td>7.7 (3.9)</td>
<td>7.7 (4.1)</td>
<td>7.8 (3.8)</td>
</tr>
<tr>
<td>Daily ON-time, hours, mean (SD)</td>
<td>6.1 (2.1)</td>
<td>6.1 (2.3)</td>
<td>6.2 (2.0)</td>
</tr>
<tr>
<td>Daily ON-time with troublesome dyskinesias, hours, mean (SD)</td>
<td>0.5 (1.1)</td>
<td>0.4 (1.1)</td>
<td>0.4 (1.1)</td>
</tr>
<tr>
<td>Daily levodopa, mg, mean (SD)</td>
<td>695 (321)</td>
<td>732 (370)</td>
<td>698 (322)</td>
</tr>
</tbody>
</table>

Concomitant PD medication, n (%)
levodopa/carbidopa | 151 (58.8%) | 148 (60.7%) | 155 (58.5%) |
levodopa/benserazide | 127 (49.4%) | 106 (43.4%) | 124 (46.8%) |
pramipexole | 95 (37.2%) | 79 (32.4%) | 96 (36.2%) |
carinopride | 72 (28.0%) | 65 (26.5%) | 69 (26.0%) |
armadafine | 59 (22.8%) | 58 (23.8%) | 55 (20.8%) |
rasagline | 30 (11.7%) | 27 (11.1%) | 39 (14.7%) |

OFF- and ON-time
- Treatment with either OPC 25mg or 50mg significantly reduced daily OFF-time (-37.4 min and -64.4 min vs. placebo; p<0.05 and p<0.001, respectively) and increased the ON-time without troublesome dyskinesia (42.7 min and 64.7 min vs. placebo; p<0.05 and p<0.001, respectively).
- No significant differences were observed for the ON-time with troublesome dyskinesia (4.1 min OPC 25 mg and 8.3 min OPC 50 mg vs. placebo; p=0.622 and p=0.317, respectively).
- When adjusted for total awake time, results were similar.
- Significantly more patients receiving either OPC 25 mg (61.4%, p<0.05) or 50 mg (67.6%, p<0.001) achieved the 2 hour OFF-time responder endpoint compared to placebo (49.0%). Similar results were observed for ON-time responders.

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

Figure 3: Change in OFF- and ON-time (% of Awake Time)

Figure 4: OFF-time Responder Rates (± 1 hour reduction)

UPDRS, Investigator’s and Subject’s Global Assessment of Change
- No significant differences compared to placebo were observed for UPDRS (UPDRS II: -2.3 -2.9 and -3.0, UPDRS III: -3.0 -4.1 and -3.5 for placebo, OPC 25 mg and OPC 50 mg respectively).
- IGAC scores improved significantly with either OPC 25 mg and OPC 50 mg vs. placebo (p=0.0145 and p=0.0428, respectively).
- SGAC scores improved significantly with OPC 25 mg (p=0.0036) while a favourable trend was observed with OPC 50 mg (p=0.0603).

CONCLUSION
- OPC 25 mg and OPC 50 mg once-daily were associated with significant improvements in motor fluctuations.
- OPC 50 mg led to greater symptomatic improvement, without significantly increasing troublesome dyskinesia.
- Results from this pooled analysis from more than 750 patients support the use of OPC as add-on to levodopa in treatment of PD patients with motor fluctuations.

References

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