A pooled analysis for 8 randomized controlled trials of istradefylline, an adenosine A_{2A} receptor antagonist: efficacy as adjunct to levodopa in Parkinson's disease (PD)

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Objective: Pooled efficacy analyses of 8 randomized, placebo-controlled studies of istradefylline combined with levodopa in PD patients experiencing motor fluctuations. Background: Istradefylline, a well-tolerated selective adenosine A_{2A} receptor antagonist, acts at sites in the indirect basal ganglia outflow pathway. In 2013, 20 and 40mg/day doses were approved for marketing in Japan as adjunctive treatment to levodopa-containing products in PD patients experiencing wearing-off. Methods: Istradefylline was evaluated in PD patients receiving levodopa with carbidopa or benserazide and experiencing motor fluctuations. Eight 12- or 16-week randomized, placebo-controlled, double-blind phase 2b/3 clinical studies were conducted globally (N=3245 subjects in total); change in OFF-time in daily, patient-completed 24-hour ON/OFF diaries provided the primary endpoint. All studies were designed to share a common methodology. Pooled analysis results from once-daily oral istradefylline (20 and 40mg/day) and placebo were evaluated using a mixed-model repeated-measures approach (including study as a factor). Results: The pooled analysis included 2719 treated subjects (placebo, n=992; 20mg/day, n=848; 40mg/day, n=879). At week 12, OFF-hours/day with 20 and 40mg istradefylline were reduced (LS mean difference from placebo in reduction from baseline [95% CI], -0.38 [-0.61, -0.15] and ‑0.45 [-0.68, -0.22], respectively). ON-hours/day without troublesome dyskinesia increased from baseline with istradefylline compared with placebo (LS mean difference from placebo [95% CI], 20mg, 0.40 [0.15, 0.66]; 40mg, 0.33 [0.08, 0.59]). Five studies showed statistical improvement in OFF time comparing istradefylline to placebo. Istradefylline was well-tolerated and average study completion rate across all 8 studies was 89%. Dyskinesia was the most frequent adverse event (8% higher incidence with istradefylline than placebo). Additional secondary outcomes will be presented. Conclusions: Istradefylline acts through an adenosine A_{2A} receptor-mediated, non-dopaminergic mechanism for PD patients experiencing levodopa-mediated motor fluctuations. In the pooled analysis of 8 studies (and in 5 individual trials), istradefylline significantly improved OFF-time and ON-time without troublesome dyskinesia.