S33.002] Safinamide Reduces L-Dopa Induced Dyskinesia and Extends ON-Time over 7 Days of Daily Dosing in the MPTP Primate Model

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OBJECTIVE: Safinamide is in phase 3 development as add-on therapy in early- and late-stage Parkinson's patients. Safinamide's combined dopaminergic and non-dopaminergic activities could affect both primary parkinsonian symptoms and treatment complications such as L-dopa induced dyskinesia (LID). This study was designed to determine whether the efficacy shown by safinamide in acute single-dose studies in a well-established preclinical model of LID is maintained with prolonged repeat dosing.

BACKGROUND: Safinamide combines potent, selective and reversible MAO-B inhibition with state-dependent sodium channel blockade, and inhibition of induced release of glutamate *in vitro*. LID is a common treatment complication in PD and is believed to be caused by non-physiologic patterns of dopamine availability in the striatum, in the context of altered plasticity and advancing neurodegeneration. Similar pathology and behavior occur in the MPTP-lesioned macaque monkey model of LID. Earlier studies showed that single oral doses of 3 to 30 mg safinamide per kg resulted in extended "on-time" and reduced dyskinesia scores in this model.

DESIGN/METHODS: Safinamide (10 mg/kg) or vehicle was administered twice daily by oral gavage for seven days. On days 1, 4 and 7, L-dopa was administered by subcutaneous injection one hour after the morning dose of safinamide, and behavior was assessed for five hours by a trained scorer blinded to the treatment.

RESULTS: On all three days, safinamide treated animals had similar, significant reductions in dyskinesia scores, and on-time was extended by an average of 38 minutes.

CONCLUSIONS: The previously reported profile of activity of safinamide in acute studies in the MPTP primate model of LID −reduction in dyskinesia scores in the presence of maintained, or even extended, anti-parkinsonian activity - was maintained over seven days without significant time-dependent changes. This activity was associated with plasma safinamide levels similar to those achieved in clinical testing. Supported by: This study was funded by Merck Serono S.A. Geneva.

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