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MEETING ABSTRACT

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Pharmacology of IRL790, a psychomotor stabilizer for the treatment of L-DOPA-induced dyskinesias and psychosis in Parkinson's disease
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The key pathophysiology of PD involves loss of dopaminergic and noradrenergic neurons in the substantia nigra and locus coeruleus, respectively, which causes severe motor symptoms. Other subcortical, cortical, and autonomic pathologies contribute to the nonmotor symptoms in PD. It has been suggested that cortico-striatal dysconnectivity and plasticity are key drivers for both core symptoms of Parkinson's disease and adverse effects emerging with long-term dopaminergic treatment.

IRL790 is a novel DA D3/D2/σ1-modulating compound, aimed at reducing levodopa-induced dyskinesias and psychosis in PD through its powerful psychomotor stabilizing properties. It is currently in phase I. IRL790 has been investigated in a series of in vivo pharmacological studies including models of disrupted dopaminergic or glutamatergic transmission. Biological measures include monoaminergic biomarkers, gene expression and behaviour.

In the monoaminergic systems, indices of increased DA turnover appear in basal ganglia and cortical regions. IRL790 also increases extracellular DA, NE and Ach levels measured by in vivo microdialysis. Furthermore, it induces frontal cortex and striatal Arc gene expression. The concomitant increase in striatal DA, DA metabolites and Arc indicates modulation of striatal DA transmission associated with enhanced signaling onto medium spiny neurons from cortico-striatal projection neurons, likely arising through inhibition of striatal DA D3 and D2 receptors.

In rat models of L-DOPA-induced adverse involuntary movements (AIMs), IRL790 significantly reduces abnormal motor behaviour, without affecting L-DOPA-induced therapeutic effects. Moreover, IRL790 has no effect on spontaneous locomotor activity over a wide dose range, but counteracts psychostimulant-induced hyperactivity. Thus in addition to antidyskinetic effects, IRL790 appears to behave as an antipsychotic. This indicates a novel compound profile with potential to alleviate LIDs and psychosis while sparing normal motor functions and L-DOPA efficacy.

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