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Tau Pathology Reduction with SM07883, a Novel, Potent, and Selective Oral DYRK1A Inhibitor

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Background: Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A overexpression in Alzheimer's disease (AD) is correlated with tau hyperphosphorylation and formation of neurofibrillary tangles (NFTs). This study assessed the potential of SM07883, an oral DYRK1A inhibitor, to inhibit tau hyperphosphorylation, aggregation, NFT formation, and associated functional phenotypes in mouse models. To assess impact on neuroinflammation, glial activation was also analyzed.

Methods: SM07883 potency was evaluated in kinase panels and tau phosphorylation (pTau) was measured in cell-based assays. To assess long-term efficacy, pTau and aggregated tau were biochemically quantified in brain stems and spinal cords lysates from 10-month-old JNPL3 mice (P301L human tau overexpression mutation in the hindbrain and spinal cord resulting in locomotor impairment) treated with SM07883 (3mg/kg, QD, n=19; 10mg/kg QD, n=13; or QoD, n=19; 3 months) or vehicle (n=20). Intracellular tau inclusions were quantified by immunostaining. Gliosis was assessed using glial fibrillary associated protein (GFAP) and Iba1 staining. A wire hanging test was used to assess motor coordination at the beginning and the end of treatment.

Results: SM07883 selectively and potently inhibited DYRK1A kinase activity (IC_{50}=2nM). In cells, SM07883 reduced pTau, especially at the DYRK1A-relevant Threonine 212 site (EC_{50}=16nM). JNPL3 mice treated with SM07883 demonstrated significant ($p<0.05$) reductions in pTau at multiple sites, aggregated forms of tau, and tau-positive intracellular inclusion staining compared to vehicle. Reduced gliosis was confirmed by ELISA ($p<0.001$) and Iba1 stains showed a significant decrease in microglial cell count compared to vehicle ($p<0.001$). SM07883 was well tolerated and treated mice had a positive net weight gain over the course of the study (1.3g +/-0.57). SM07883-treated mice showed a reduction of the clinical signs. Motor function in the wire hanging test was significantly improved in SM07883-treated JNPL3 mice compared to vehicle ($p=0.048$).

Conclusion: SM07883, a selective, potent, and oral DYRK1A inhibitor currently being tested in a clinical trial, significantly reduced tau phosphorylation, pathological tau overexpression and associated neuroinflammation, and improved functional endpoints compared to vehicle. SM07883 has potential as a treatment for chronic tauopathies such as AD.