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## **SM07883, a novel oral DYRK1A kinase inhibitor, reduced tau, amyloid pathology, and related inflammation in preclinical models**

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**Background:** Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) overexpression in Alzheimer's Disease (AD), Down Syndrome, and Progressive Supranuclear Palsy is correlated to the presence of tau hyperphosphorylation, tau aggregates, and neurofibrillary tangles (NFTs) as well as pathological amyloid fragments and plaque formation. This study assessed the potential of SM07883, an oral DYRK1A inhibitor, to inhibit phosphorylation of tau and amyloid precursor protein (APP), NFT or amyloid plaque formation, and associated functional phenotypes in transgenic mouse models.

**Methods:** Tau phosphorylation (pTau), APP phosphorylation (pAPP), and generation of beta-amyloid was measured in cell-based assays. To assess long-term efficacy, pTau, oligomeric tau, and aggregated tau were biochemically quantified in brain stems and spinal cords from JNPL3 mice (P301L human tau overexpression mutation) treated with SM07883 or vehicle (3mg/kg, QD, 3 months). 3xTg-AD (APP, PSEN/P301L tau) female mice were treated with SM07883 or vehicle (5mg/kg, QD, 6 months) and the hippocampi were analyzed for NFT-containing cells, amyloid load, and gliosis evaluated by immunostaining with Western blot quantification. Motor coordination was evaluated using a wire hanging test in JNPL3 mice. Cognitive behavior was measured using the Y maze and Novel Object Recognition paradigm in 3xTg-AD mice.

**Results:** In cells, SM07883 reduced pTau at Thr212 and pAPP at Thr668 ( $EC_{50} = 16\text{nM}$  and  $137\text{nM}$ , respectively). JNPL3 mice treated with SM07883 demonstrated significant reductions in tau hyperphosphorylation, oligomeric and aggregated tau, and NFT staining compared to vehicle ( $p < 0.05$ ). Hippocampi from 3xTg-AD mice treated with SM07883 showed reduction in amyloid load,  $A\beta$  fragments, aggregated tau, and pTau compared to vehicle ( $p < 0.05$ ). In both models, SM07883 treatment reduced gliosis immunoreactivity compared to vehicle that was confirmed by Western blot ( $p = 0.001$ ). Compared to vehicle, SM07883 significantly improved motor function in the wire hanging test in JNPL3 mice and prevented cognitive decline in 3xTg-AD mice ( $p < 0.05$ ).

**Conclusion:** These effects on tau, amyloid, and inflammation suggest that SM07883 has potential as a treatment for chronic tauopathies, including AD.