Tau Pathology Reduction with SM07883, a Novel, Potent, and Selective Oral DYRK1A Inhibitor - a Potential Therapeutic for Alzheimer’s Disease

Benoît Melchior, Carolyn Lai, Karen Duong-Polk, Amanda Tjitro, Deniz C. Ince, Joshua Stewart, Luis Dellamary, Brian Hofilena, Gopi Mittapalli, Sunil KC and Yusuf Yaziçi

Samumed, LLC, San Diego, CA

Background: Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1a) overexpression in Alzheimer’s Disease (AD) is correlated to Tau hyperphosphorylation, formation of oligomers, and neurofibrillary tangle (NFT) formation. 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. Glial activation was also analyzed to assess potential impact on neuroinflammation.

Methods: SM07883 selectivity and potency was evaluated in kinase panels and Tau phosphorylation (pTau) was measured in cell-based assays. SM07883 pharmacodynamics were measured in wild type (WT) mice. To assess long-term efficacy, pTau, oligomeric and aggregated Tau were biochemically quantified in brain stems and spinal cords from ten-month-old JNPL3 mice (P301L human Tau overexpression mutation) treated with SM07883 or vehicle (3mg/kg, QD, 3 months). NFT-containing cells were detected and quantified by immunostaining. Astrocyte activation was assessed using glial fibrillary associated protein (GFAP) staining with Western Blot quantification. Motor coordination was evaluated biweekly using a wire hanging test.

Results: SM07883 selectively and potently inhibited DYRK1a kinase activity (IC₅₀ = 2nM). In cells, SM07883 reduced pTau at the Threonine 212 site (EC₅₀ = 16nM). In pharmacokinetic studies, SM07883 demonstrated good exposure across multiple species (mouse brain: plasma ratio > 3). Compared to vehicle, WT mice showed a dose dependent reduction of transiently induced brain pTau in a pharmacodynamic model starting with a single, 1.25mg/kg SM07883 dose (47%, p=0.0002). JNPL3 mice treated with SM07883 demonstrated significant (p<0.05) reductions in Tau hyperphosphorylation, oligomeric and aggregated Tau, and significantly lower NFT staining compared to vehicle. Reduced GFAP immunoreactivity was confirmed by Western Blotting (37%, p=0.0010). SM07883 was well tolerated with weight gain over the 3 month treatment period and reduced morbidity and mortality in treated animals compared to vehicle. Motor function in the wire hanging test was significantly improved in SM07883-treated JNPL3 mice compared to vehicle (p=0.034) starting 5 weeks after treatment initiation.

Conclusion: SM07883, a selective and potent, oral, brain-penetrant, DYRK1a inhibitor significantly reduced Tau phosphorylation, the effects of pathological Tau overexpression, and neuroinflammation, and improved functional endpoints compared to vehicle. SM07883 has potential as a treatment for chronic tauopathies such as AD.