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SM07883, a Novel, Oral DYRK1A Kinase Inhibitor, Reduced Tau Pathology and Associated Behavioral Deficits in Preclinical Models

Benoît Melchior, PhD, Karen Duong-Polk, Carolyn Lai, Bora Güner, Stacy Habroun, MS, Yusuf Yazici, MD

Samumed, LLC, San Diego, CA

Background: In tau-associated neurodegenerative diseases, overexpression of dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is correlated with tau hyperphosphorylation, tau aggregates, and neurofibrillary tangles. These pathologies are correlated with behavioral deficits, including cognition and motor function. This study assessed SM07883, a small-molecule, oral DYRK1A inhibitor, and its potential to inhibit tau phosphorylation and prevent associated functional phenotypes in transgenic mouse models.

Methods: Motor function was evaluated using a wire hang test in JNPL3 mice (P301L human tau overexpression mutation) treated with SM07883 (3mg/kg, PO, QD, 3 months) or vehicle. Tau phosphorylation (pTau), oligomeric tau, and aggregated tau were biochemically quantified in brain stems and spinal cords from JNPL3 mice treated with SM07883 or vehicle. In a small exploratory study, tau-positive inclusions and gliosis were analyzed by immunostaining quantification in hippocampi from 3xTg-AD mice (APP, PSEN, P301L tau) treated with SM07883 (5mg/kg, PO, QD, 6 months) or vehicle. Short-term spatial working memory and recognition memory were measured using the Y maze spontaneous alternation test and Novel Object Recognition (NOR) paradigm, respectively, in 3xTg-AD mice. pTau was measured in human tau/DYRK1A-transfected HEK-293T cells and human neuroblastoma cells.

Results: Daily administration of SM07883 reduced tau pathology and functional deficits in transgenic mouse models. SM07883 significantly improved motor coordination in the wire hang test in JNPL3 mice ($P<0.05$) compared to vehicle. SM07883 also significantly reduced tau hyperphosphorylation, oligomeric tau, aggregated tau (spinal cords), and tau-positive inclusions in brain stems ($P<0.05$) from these mice. In 3xTg-AD mice, SM07883 demonstrated a similar trend in reducing aggregated tau and tau-positive inclusions in hippocampal areas. SM07883 significantly reduced tau-induced neuroinflammation ($P<0.05$) in JNPL3 and 3xTg-AD mice compared to vehicle. In 3xTg-AD mice, SM07883 reduced cognitive deficits in the NOR test and Y maze compared to vehicle. *In vitro* assays confirmed that SM07883 reduced DYRK1A-mediated pTau at Thr212 (EC_{50}=16 nM), Ser202/Thr205 (EC_{50}=69 nM), Thr181 (EC_{50}=127 nM), and Ser396 (EC_{50}=200 nM).

Conclusion: In preclinical models, daily oral administration of SM07883 reduced tau pathology, decreased neuroinflammation, and improved functional deficits compared to vehicle. SM07883 has potential as a treatment for chronic tauopathies. A Phase 1 human study is ongoing.