SM0783, A NOVEL, POTENT, AND SELECTIVE ORAL DYRK1A INHIBITOR REDUCED TAU PATHOLOGY IN PRECLINICAL MODELS

Benito Melchior, PhD, Carolyn Lai, Karen Duong-Polk, Amanda Tijfo, Lauren Pitzer, Joshua Stewart, Luis Dellamaria, Scott Anderson, Brian Hoflierna, Gopi Mittapalli, PhD; Sunil KC, PhD, Philippe Marchand, PhD, and Yusuf Yazici, MD
Samumed LLC, San Diego, CA

Background

• Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression in Alzheimer’s and Pick’s Disease was correlated to Tau hyperphosphorylation, oligomer, and neurofibrillary tangle (NFT) formation.
• Elevated cellular stress signals (e.g. Aβ, TNFα) induce DYRK1A activity2–6 which then contributes to Tau pathology.7
• A potential therapeutic for tauopathies, SM0783 (novel, small molecule, DYRK1A inhibitor) was evaluated in preclinical models, compared to controls, for: - Inhibition of Tau hyperphosphorylation, aggregation, and NFT formation in a Tau transgenic mouse model - Effects on Tau-associated functional phenotypes - Effects on neuroinflammation - Pharmacokinetic and pharmacodynamic properties

Results

• SM0783 is a potent DYRK1A inhibitor with novel selectivity profile and therapeutic brain and CSF exposures after oral administration in mice
• In preclinical models compared with vehicle, SM0783: – Reduced Tau pathology (pTau aggregation, NFTs) – Improved functional deficits and health of Tau transgenic mice – Reduced associated neuroinflammation – SM0783 may provide therapeutic, disease modifying effects in tauopathies

Methods

• SM0783 selectivity/potency was evaluated in a 460 kinase inhibition panel
• Tau phosphorylation (pTau) inhibition was measured in human Tau/DYRK1A transfected HEK293T cells and human neuroblastoma cells
• Pharmacokinetics in brain, cerebral spinal fluid (CSF) and plasma were analyzed in wild-type (WT) mice after single administration of oral or intravenous SM0783
• Pharmacodynamics were measured in WT mice in an anesthesia-induced transient Tau hyperphosphorylation model with brain lysates quantified using Western Blot for pTau
• Cytokines were measured in plasma and brain tissue by electrochemiluminescence (MesoScale Discovery) from WT mice after stereotaxic injection of LPS/IFNγ
• SH-SY5Y human neuroblastoma cells were treated for 16 hours with DMSO, 1.1µM of a potent CLK inhibitor (Cmpd #79, patent US20160008365A1; CLK2 IC50: 9nM) or 1.1µM of SM0783 and the respective cDNA was used to amplify specific regions of the MAPT gene. Reverse transcription polymerase chain reaction (RT-PCR) was used for identification of splicing (3R) or inclusion of exon 10 (4R). Quantity of 3R/4R was by densitometry for a ratio over total amount of Tau cDNA in the samples, N=2 per condition.

Conclusions

• Ten-month-old JNPL3 mice (P301L human Tau overexpression mutation) were orally administered SM0783 or vehicle (3 mg/kg, QD, 3 months)
  – General tolerability was assessed monitoring weight, morbidity and mortality. Motor coordination was evaluated after dosing using a wire hang test.10
  – pTau, oligomeric and aggregated Tau were biochemically quantified in brainstems and spinal cords. Tau-positive inclusions were detected and quantified by immunostaining with a Ser202/Thr205 (AT8 clone) antibody at 13 months
  – Glial activation was assessed in brainstems using glial fibrillary associated protein (GFAP) staining

References