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## **Cognitive Improvement and Protection Against Amyloid and Tau Pathology with SM07883, an Oral DYRK1A Inhibitor, in the 3xTG Mouse Model of Alzheimer's Disease; Preliminary Results**

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**Objectives:** Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) regulates APP and tau phosphorylation, is overexpressed in Alzheimer's Disease (AD) brains, and correlates with disease pathology. DYRK1A inhibition may reduce AD pathology. This preliminary study assessed the effects of SM07883, a small-molecule DYRK1A inhibitor, on amyloid, tau, and neuroinflammation pathology together with cognition in a mouse AD model.

**Methods:** Ten-month-old female 3xTg (APP/PSEN/Tau P301L) mice were orally administered SM07883 (QD, 5mg/kg) or vehicle for 183 days. Mice were assessed for cognitive behavior in the Novel Object Recognition (NOR) and Y Maze spontaneous alternation tests. At termination, brains were analyzed for amyloid by histology. Hippocampal area lysates were analyzed for tau and APP phosphorylation, amyloid and tau fragments, and gliosis (GFAP) by Western blot and ELISA.

**Results:** 3xTg mice had elevated tau, APP phosphorylation, and astrogliosis in the hippocampal area. All SM07883 results were compared to controls at termination in these pilot studies. A reduction of elevated tau and APP phosphorylation at Thr668 ( $p < 0.05$ ) was observed. Both amyloid ( $p < 0.05$ ) and tau fragments were reduced in hippocampal lysates. Immunostaining showed amyloid reduction in the hippocampal area. GFAP analysis showed a reduction of neuroinflammation (gliosis). Daily SM07883 improved NOR ( $p < 0.01$ ) and prevented cognitive deficit in the Y Maze.

**Conclusion:** In preliminary studies, daily oral administration of SM07883 (a DYRK1A inhibitor) in triple-transgenic mice showed reduction of pathological AD hallmarks (tau and amyloid) and protected against the cognitive deficits compared to vehicle. Full study results will be presented at this meeting.