TAU PATHOLOGY REDUCTION WITH SM07883, A NOVEL, POTENT, AND SELECTIVE ORAL DYRK1A INHIBITOR – POTENTIAL THERAPEUTIC FOR ALZHEIMER’S DISEASE

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Background

• Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression in Alzheimer’s (AD) and Pick’s Disease has been correlated to Tau hyperphosphorylation, oligomer, and neurofibrillary tangle (NFT) formation.

• Elevated cellular stress signals (e.g., Aβ, TNFα) induce DYRK1A activity, which then contributes to Tau pathology.

• A potential therapeutic for AD, SM07883 (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

Conclusions

• SM07883 is a potent DYRK1A inhibitor with a novel selectivity profile and therapeutic brain and CSF exposures after oral administration in mice.

• In preclinical models compared with vehicle, SM07883:
  – Reduced Tau pathology (pTau, aggregation, NFTs)
  – Improved functional deficits and health of Tau transgenic mice
  – Reduced associated neuroinflammation

• SM07883 may provide therapeutic, disease-modifying effects in AD

Results

Figure 1. SM07883 potently inhibited DYRK1A kinase activity with a novel selectivity profile

Figure 2. SM07883 potently inhibited DYRK1A-mediated Tau hyperphosphorylation in vitro

Figure 3. SM07883 inhibited Tau pathology in JNPL3 Tau mice

Figure 4. SM07883 improved motor function, weight, and general health of JNPL3 Tau mice

Figure 5. SM07883 reduced Tau-induced glial activation (neuroinflammation) in JNPL3 mice

Figure 6. SM07883 was orally bioavailable and brain penetrant in mice with an apparent log-linear correlation between brain, plasma, and CSF

Figure 7. SM07883 reduced Tau phosphorylation in the mouse brain

Methods

• SM07883 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 SM07883.

• Pharmacokinetics were measured after a single oral dose of SM07883 in WT mice in an anesthesia-induced transient Tau hyperphosphorylation model with brain lysates quantified using Western Blot for pTau.

• Tau- and/or pThr212–positive inclusions were detected and quantified by immunostaining with a pSer202/Thr205 (AT8) antibody at 13 months in formalin-fixed brains.

• General tolerability was assessed monitoring weight, morbidity, and mortality. Motor coordination in mice was evaluated after dosing using a wire hang test.

References