REDUCTION OF BETA AMYLOID PRODUCTION IN VITRO AND IN VIVO BY NOVEL SMALL MOLECULE BACE1 INHIBITORS

S. Gustavsson¹, S. Eketjäll¹, B. Georgievskà¹, J. Janson², J. Neelissen², F. Jeppsson¹, B.-M. Swahn³, P. Söderman³, J. Fältling⁴

¹Neuroscience, ²DMPK, ³Medicinal Chemistry, ⁴AstraZeneca R&D Södertälje, Södertälje, Sweden

Introduction: Inhibiting beta amyloid (Aβ) production by targeting the beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) that cleaves APP to generate Aβ is an approach for therapeutic intervention in Alzheimer’s disease (AD). Small molecule BACE1 inhibitors are expected to decrease Aβ-peptide generation and thereby reduce amyloid plaque formation in the brain, a hallmark neuropathological lesion in AD.

Aims: In the present study, pharmacokinetic and pharmacodynamic (PK/PD) properties of novel small molecule AZ BACE1 inhibitors were evaluated in vitro and in vivo.

Methods: Potent and selective inhibitors of human BACE1 were characterized in vitro using cell lines and primary mouse cortical neurons, and in vivo using C57BL/6 mice receiving vehicle or BACE1 inhibitors as a single dose via oral gavage.

Results: The small molecule AZ BACE1 inhibitors were potently inhibiting BACE1-mediated APP-cleavage and thereby reducing Aβ production from APP-expressing cell lines. Selectivity against BACE2 and Cathepsin D was also achieved with these inhibitors. Furthermore, the BACE1 inhibitors displayed a concentration-dependent inhibition of Aβ release in primary mouse cortical neurons. In addition, C57BL/6 mice receiving the inhibitors demonstrated a dose-dependent decrease of Aβ levels in brain and plasma. The IC₅₀ in primary mouse cortical neurons corresponded to the effective free brain concentration in vivo.

Conclusions: These results strongly support BACE1 inhibition as a feasible approach for therapeutic intervention in AD.