PRESENLIN 1 (PS1) SELECTIVE GAMMA-SECRETASE INHIBITORS; EFFICACY AND TOLERABILITY IN PS2 DEFICIENT AND WILD TYPE MICE


1AstraZeneca, 2AstraZeneca R&D Södertälje, Södertälje, 3Karolinska Institutet, Stockholm, Sweden, 4Flanders Interuniversity for Biotechnology, Leuven, Belgium

Introduction: γ-Secretase plays a pivotal role in Alzheimer Disease related Ab peptide generation and is also involved in Notch signaling and other important cell signaling pathways. Several classes of γ-secretase inhibitors have been developed to target Ab production, many of which causes mechanism based toxicity due to disturbed Notch signaling. The inhibitor MRK-560 belongs to a few exceptions, which display both efficacy and tolerability in vivo. The molecular basis of the therapeutic window of MRK-560 is not known, but in vitro pharmacological studies suggest that MRK-560 displays a preference for Presenilin 1 (PS1) expressing γ-secretases.

Aim: To explore whether preference for PS1 γ-secretase complexes results in improved therapeutic index.

Methods: Explore efficacy and tolerance of MRK-560 in wt and PS2 ko mice.

Results and conclusions: MRK-560, given once daily for 4 days at two different doses, resulted in similar plasma and brain exposure levels and reduction in brain and plasma Ab levels in both wt and PS2 ko mice. Interestingly, while the compound was well tolerated in wt mice, globet cell metaplasia, thymus atrophy and spleen marginal zone depletion were observed in PS2 ko mice. Moreover, Notch signaling was inhibited to a larger extent in jejunum in PS2 ko as compared to wt mice. Combined these data suggest that PS2 plays a major role in mediating essential γ-secretase signaling in the periphery and that inhibitors with a preference for PS1 γ-secretases provide CNS efficacy while sparing essential peripheral γ-secretase signaling.