E2012, A NOVEL GAMMA-SECRETASE MODULATOR, DECREASES PLASMA AMYLOID-BETA (Aβ) LEVELS IN HUMANS

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Introduction: Senile plaques of Alzheimer's Disease (AD) consist predominantly of Aβ40 and Aβ42. Reduction of Aβ levels in brain, particularly Aβ42, has been suggested as a therapeutic strategy for AD.

Aims: E2012, a novel gamma-secretase modulator, inhibits the production of Aβ42 and Aβ40 in vitro without inhibiting the cleavage of Notch. Here we report the pharmacokinetic (PK) and pharmacodynamic (PD) results from a single ascending dose study with E2012 in humans.

Methods: Healthy human subjects received single oral doses of 1, 2.5, 5, 10, 20, 50, 100, 200, 300 or 400 mg E2012, or placebo. Plasma concentrations of E2012, Aβ(x-40), and Aβ(x-42) were measured. PK and PD parameters were calculated.

Results: E2012 reduced plasma Aβ40 and Aβ42 in healthy subjects in a dose-related manner. Aβ42 decreased to a greater extent than Aβ40 (maximum reductions at 400 mg ~ 50% and ~30%, respectively) at 4-6 hrs post-dose, without a rebound effect. AUC0-inf increased proportionally up to 400 mg. Cmax increased proportionally up to 200 mg and less than proportionally thereafter. Results from rat studies with E2012 were predictive of the results obtained in humans for plasma Aβ effect over 24 hr. Effects on rat CSF and brain Aβ followed similar trends, supporting the use of CSF as a surrogate matrix for effects on brain Aβ in humans.

Conclusion: E2012 differentially reduces plasma Aβ40 and Aβ42 in healthy subjects following single oral doses, suggesting that gamma-secretase modulation may achieve substantial reductions in toxic Aβ species without the deleterious effects of Notch inhibition.