BMS-708163, A NOTCH-SPARING GSI, DECREASES CENTRAL ABETA IN RATS, DOGS, AND HUMANS WITH A THERAPEUTIC MARGIN RELATIVE TO NOTCH TOXICITY

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Introduction: A leading hypothesis for Alzheimer's disease (AD) is the amyloid hypothesis, which states that Abeta is required for the initiation and progression of AD. Since cleavage of the amyloid precursor protein (APP) by gamma-secretase is required to form Abeta, gamma-secretase inhibitors (GSI) are an attractive therapeutic approach for AD. In addition to APP, gamma-secretase cleaves other proteins including the Notch proteins which control cell fate in several tissues, such as the gastrointestinal tract and spleen.

Aim: To develop a GSI that will allow clinical evaluation of the amyloid hypothesis.

Methods: In vitro potency and selectivity were determined using cellular assays. In vivo Abeta levels and toxicity were determined in rats and dogs. Safety, tolerability, and Abeta levels were determined in healthy volunteers.

Results: BMS-708163 inhibited Abeta40 generation (IC\(_{50}\) = 0.30 ± 0.15 nM) and Notch signaling (IC\(_{50}\) = 58 ± 23 nM) in vitro yielding a Notch/APP selectivity ratio of 193X. In contrast, a non-selective GSI, semagacestat, was 40-fold less potent (Abeta40 IC\(_{50}\) = 12 ± 1 nM) and 15-fold less selective (Notch/APP = 13X). BMS-708163 robustly and similarly decreased brain and CSF Abeta in rats and dogs at doses without Notch-dependent GI or spleen toxicity. Likewise, BMS-708163 decreased CSF Abeta more than 50% without evidence of Notch-dependent toxicity in single and multi-dose (28 day) studies in healthy volunteers.

Conclusion: These results support the further development of BMS-708163 for treatment of AD.