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VIEWPOINT

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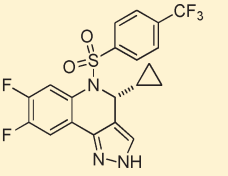
ACS Chemical Neuroscience Molecule Spotlight on ELND006: Another γ-Secretase Inhibitor Fails in the Clinic

Corey R. Hopkins

Department of Pharmacology and Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Vanderbilt University, Nashville, Tennessee 37232-6600, United States

ABSTRACT: ELND006 is a novel γ-secretase inhibitor by Elan Corporation that was in the clinic as a potential treatment for Alzheimer's disease (AD). The clinical trial for ELND006 was halted in October 2010 due to liver side effects that are thought to be unrelated to the mechanism of action. However, this represents another small molecule γ-secretase inhibitor that has failed in clinical trials (semagacestat) (http://newsroom.lilly.com/releasedetail.cfm?releaseid=499794) which raises serious questions regarding this mechanism for the treatment of AD.

KEYWORDS: Alzheimer's disease, γ-secretase, clinical trials, ELND006, semagacestat



ELND006
Elan's γ-Secretase inhibitor

Alzheimer's disease (AD) is a progressive neurodegenerative disease which has no known cure and very few treatment options. AD affects >5 million Americans, making it the most common neurodegenerative disorder. One telltale sign of AD is the accumulation of amyloid plaques and neurofibrillary tangles which are thought to contribute to the degradation of neurons leading to worsening of the symptoms of AD. Two general areas of research toward finding effective treatments for this devastating disease concentrate on the presence of these amyloid plaques and neurofibrillary tangles. The latter are insoluble twisted fibers consisting (predominantly) of the protein tau which helps to form a microtubule. In AD, the tau protein is abnormal, leading to a collapse of the microtubule (tau hypothesis).[2] The former, and widely held, hypothesis is that an imbalance exists between the production and removal of Aβ peptides, a 40−42 residue found in the amyloid plaques.[3] These Aβ peptides are generated by the action of membrane-bound β-amyloid precursor proteins (APP) by β-secretase (BACE) and then by γ-secretase. In this process, both Aβ40 and Aβ42 are generated (generally more Aβ40); however, the production of Aβ42 is more closely related to the disease state of AD.[4] There have been numerous studies showing that inhibiting γ-secretase leads to lower levels of Aβ in the brains of transgenic and nontransgenic mice.[5] However, due to the complexity of the process, inhibition of γ-secretase also can lead to inhibition of other proteins, namely, Notch, which has been shown to be embryonic lethal, generating concern regarding the selectivity of these compounds.

ELND006 is one of the newest molecules to be reported on regarding the testing of the β-amyloid hypothesis. Unfortunately, no molecule has made it far enough to ultimately test this hypothesis. Semagacestat, a unique γ-secretase, from Eli Lilly and Company[6] was the most recent molecule to fail in clinical trials. Semagacestat was tested in a >3000 patient phase III clinical trial; unfortunately, this compound performed worse than placebo. Although limited preclinical data has been published on ELND006, it has been reported to be more selective than semagacestat. A number of closely related analogues have been reported in the literature with a des-fluoro analogue showing an IC_{50} = 0.7 nM.[7] ELND006 was not exemplified in this communication; however, limited data was presented at the 2010 Alzheimer's Association International Conference on Alzheimer's Disease in which ELND006 was reported to have an in vitro IC_{50} = 0.34 nM against APP and IC_{50} = 5.3 nM versus Notch signaling.[8] Cell based data was also presented against APP and Notch (IC_{50} = 1.1 and 82 nM, respectively). ELND006 was shown to reduce Aβ-levels up to 50% in the cerebrospinal fluid. ELND006, however, did show significant side effects in the liver, and further clinical evaluation was halted in the fall of 2010.[9] Elan reported that the side effects were not due to the mechanism of action. Although there are several well publicized clinical failures of γ-secretase inhibitors (tarenflurbil, semagacestat, ELND006), industrial research interest in γ-secretase inhibitors remains high with several compounds in various stages of development (BMS, Elan, etc.). However, it still remains to be seen whether the β-amyloid hypothesis bears any fruit as a viable treatment option for AD.

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