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Viewpoint

# ACS Chemical Neuroscience Molecule Spotlight on Semagacestat (LY450139)

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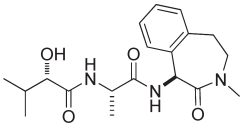
## Abstract



Semagacestat (LY450139)
γ-secretase inhibitor

Semagacestat (LY450139) is a novel γ-secretase inhibitor currently in late-stage development by Eli Lilly and Company as a potential treatment for Alzheimer's disease (AD). Semagacestat is currently being studied in two phase III clinical trials.

**Keywords:** Gamma-secretase, Alzheimer's disease, AD, neurodegeneration, LY450139, semagacestat

Semagacestat (LY450139) is a novel, small molecular weight inhibitor of γ-secretase that is currently in late-stage development by Eli Lilly and Company for the treatment of Alzheimer's disease. Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia (*1*). AD is the leading neurodegenerative disease, is estimated to affect as many as 5.3 million Americans, and a disease that has no known cure. A hallmark of AD is extracellular amyloid plaques, composed mainly of 40−42 residue β-amyloid peptides (*2*). In this, now widely accepted hypothesis, an imbalance between the production and removal of Aβ peptides is believed to exist leading to an increased level of Aβ, and it is the high levels of Aβ that triggers a series of events that lead to neuronal dysfunction and dementia (*3*). This hypothesis has spurred the research into finding drugs that prevent Aβ formation (*4*).

Aβ peptides are generated by the cleavage of membrane-bound β-amyloid precursor proteins (APP) by, first, the action of β-secretase (BACE, an aspartyl protease), and second, γ-secretase. Within the process of APP, more Aβ40 than Aβ42 are generally produced; however, it is Aβ42 that is more closely related to AD (*5*). A number of studies have shown that γ-secretase inhibitors lower the levels of Aβ in the brain of transgenic APP-expressing mice, as well as in nontransgenic mice (*3*). These results for the inhibition of γ-secretase have strengthened the strategy for the use of inhibitors of this target for the potential treatment of AD; however, γ-secretase is also involved in processing a variety of other proteins, including Notch, and it is this signaling process that has shown to, when knocked-out (i.e., knockout of PS1−Notch signaling), be embryonic lethal, raising concern that inhibition of this enzyme complex could lead to side effects due to the reduction in Notch signaling (*6*).

Despite this potential side-effect profile and hence the potential restriction of the clinical use, semagacestat (LY450139) has been taken into clinical trials by Eli Lilly and Company. Previously reported clinical trials with semagacestat (LY450139) have shown the drug to have short-term reduction in plasma Aβ40 levels in healthy patients and those with AD up to 40% using single daily dosing (*7*, *8*). Semagacestat was also studied in a dose-escalation study in healthy volunteers and was shown to demonstrate a dose-dependent increase in drug levels in plasma and cerebrospinal fluid (CSF) as well as a dose-dependent reduction in plasma Aβ levels (*9*). In a recently completed phase 2 safety trial with semagacestat (LY450139), the plasma Aβ40 concentration was reduced by 58% and 65% for the 100-mg and 140-mg groups, respectively (*10*). The drug was generally well tolerated at doses up to 140-mg/day for 14 weeks, although it was reported that several findings indicate the need for close clinical monitoring (*10*). Although there was significant Aβ reductions in plasma (consistent with the inhibition of γ-secretase), no significant reduction was seen in CSF Aβ levels. On the basis of these results, Eli Lilly recently reported that semagacestat (LY450139) has entered into two-phase III clinical trials (IDENTITY and IDENTITY-2) to assess the effect on the progression of AD. The enrollment for IDENTITY was completed in the last quarter of 2009, with the

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enrollment of IDENTITY-2 expected to be completed by mid-2010. The results of these trials will be much anticipated for this novel mechanism for a potential disease modifying treatment for AD.

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