Evaluate Vantage

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Will gamma secretase Alzheimer's class survive the fall of semagacestat?

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Eli Lilly's failed trial for the Alzheimer's drug, semagacestat, raises questions about whether the gamma secretase inhibitor class of compounds, and indeed the whole approach of targeting the beta-amyloid (A-beta) plaque, can reverse the course of the degenerative disease. Semagacestat is the second high profile failure of a gamma secretase candidate after Flurizan bombed out in similar fashion two years ago, indicating perhaps that inhibiting production of the amyloid precursor protein does not improve prognosis (*Flurizan failure highlights Myriad's diagnostic potential, June 30, 2008*).

The gamma secretase inhibitor class is, or was, regarded as promising and important in the battle to develop a disease modifying therapy for Alzheimer's. While Lilly is hurting after this latest pipeline setback, hopes and attention now turn to the next most advanced candidates in the class (see table below), foremost of which is Bristol-Myers Squibb's BMS-708163 - phase II data from a recently completed trial should be available by year-end and is now even more important for the gamma secretase approach to have a realistic future.

Hopes fading

In the overall Alzheimer's disease pipeline, semagascestat represented the second most valuable asset and is the third-most-valuable candidate in Lilly's pipeline at $780m, according to *EvaluatePharma's NPV Analyzer*. Even with heavily risk-adjusted sales of $325m by 2016, it was forecast to be an important growth driver for the group.

The Indiana-based company is fortunate to have such drugs as Alimta, Humalog, Cialis and Effient to carry some weight. Yet it is facing one of the steepest patent cliffs in the industry, with such heavy hitters as Zyprexa and Cymbalta losing patent protection in the next three years.

The semagacestat trial is one of three body blows the company has suffered in recent weeks. A US court invalidated Lilly's patent on the attention deficit hyperactivity disorder drug Strattera more than six years early (*Eli Lilly needs to win battles like Strattera, August 13, 2010*) and also lost a patent decision on Gemzar in July. In addition, FDA staff advisers have questioned the data Lilly used to support adding a chronic pain indication to Cymbalta, which is before an FDA advisory committee August 19 (*Event - Lilly looks to Cymbalta expansion, August 11, 2010*).

The slow drip of bad product news is bound to affect the company's shares – they lost 2% yesterday – and a negative vote on Cymbalta's chronic pain indication will only exacerbate market worries.

In a release, Lilly executives expressed support for the remaining late-stage a-beta drug, solanezumab, an anti a-beta monoclonal antibody, similar to Elan/Pfizer/J&J's bapinezumab which despite its own clinical setbacks continues to hold the most hopes for validating the A-beta hypothesis (*Therapeutic focus - Hopes for Alzheimer's placed firmly on A-beta, June 11, 2008*).

Getting worse

In two studies covering 2,600 patients with at the mild or moderate stage of disease progression, the Lilly trials showed that the patients taking semagacestat actually worsened when compared to those taking placebo on primary endpoints of cognition and activities of daily living, and also found an association with increased risk of skin cancer.

When Flurizan failed it showed no statistical difference with placebo in terms of cognitive functions – meaning the Flurizan patients did not decline any faster than those taking placebo - and the belief was that the drug may not have been potent enough. That semegacestat patients turned out worse is a mystery, and the root of its failure may not be known until researchers can have a look at such data as PET scans of subject brains and follow up appointments assessing long-term cognitive effects.

Weakening shots

Following the failure of semegacestat, Flurizan, and also TorreyPines Therapeutics/Eisai's E2012, which had also attracted some hope as a more potent inhibitor than Flurizan, the class is struggling to produce any graduates that make the grade.

A phase II study of BMS-708163 in 200 patients with mild to moderate Alzheimer's disease completed in June, according to clinicaltrials.gov, so results should be released within the next couple of months. The trial is mainly assessing the drug’s safety and tolerability although a number of secondary efficacy outcomes, such as cognition and daily living activities scales, are included.

A second phase II trial is currently recruiting up to 270 patients with prodromal Alzheimer's disease, the earliest stage of the disease when patients experience memory loss or mild cognitive impairment. Again the study is mainly looking at safety and tolerability, although secondary outcomes will assess the predictive value of CSF biomarkers (Aß40, Aß42, total Tau, phosphorylated Tau) on progression to dementia. The study is expected to complete by the end of 2012.

Meanwhile Humanetics, in collaboration with the Mount Sinai School of Medicine, successfully completed a phase IIa trial of NIC5-15 in June last year. A phase IIb trial was expected to start by the end of last year, although the privately-held company has not yet announced or confirmed this has happened and no record of the trial appears on clinicaltrials.gov.

Gamma secretase inhibitors - clinical stage candidates

Status	Product	Company	Originator	Launch WW	Sales in 2016 ($m)
Phase III	Semagacestat (LY450139)	Eli Lilly	Eli Lilly	2012	325
Phase II	BMS-708163	Bristol-Myers Squibb	Bristol-Myers Squibb	2014	27
	NIC5-15	Humanetics	Mount Sinai School of Medicine	-	-
Phase I	ELND-006	Elan	Elan	-	-
	Begacestat (PF-5212362)	Pfizer	Wyeth	-	-
	SRA-444	Pfizer	Wyeth	-	-
	CHF 5074	Chiesi	Chiesi	-	-