Evaluate Vantage

September 02, 2016

All the elements of an Alzheimer's bubble – but look out for December

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Alzheimer's disease remains the riskiest of bets in biopharma, and yet repeated failure, long development timelines and complex trials are all counterbalanced by one simple fact: regulators appear eager to entice companies to keep trying.

Case in point: Biogen's aducanumab being granted fast-track status by the US FDA in spite of an inconsistent efficacy showing so far and a toxicity profile that correlates with people genetically predisposed to the disease. Alzheimer's is looking like it will see a late-2016 bubble as the sector awaits results of Lilly's Expedition-3 trial of solanezumab later this year (see table below).

Regulators have obvious reason to encourage research in this field. Prevalence is expected to rise with an aging population, and the approved drugs have modest efficacy. Acetylcholinesterase inhibitors like Aricept have shown an effect on cognitive tests, but their ability to delay disability or the need for institutional care has been challenged.

Thus in spite of trial results that would have felled projects in heart disease or diabetes, for example, Lilly has soldiered on with solanezumab in the Expedition 3 programme. Biogen, meanwhile, has skipped over phase II to take aducanumab into pivotal study following the Prime trial.

Indeed, most of the phase III pipeline in Alzheimer's disease consists of agents that at best have offered modest benefits in earlier tests, or have completely missed the mark – witness Roche also persisting with crenezumab and gantenerumab.

Late-stage Alzheimer's projects			
Project	**Company**	**Pharmacology class**	**2022 sales ($m)**
Solanezumab	Eli Lilly	Amyloid beta MAb	1,556
Verubecestat	Merck & Co	BACE 1 inhibitor	1,480
Intepirdine	Axovant Sciences	5-HT6 (serotonin) antagonist	1,459
Aducanumab	Biogen	Amyloid beta MAb	939
Crenezumab	Roche	Amyloid beta MAb	531
Idalopirdine	Lundbeck/Otsuka Holdings	5-HT6 (serotonin) antagonist	342
Lanabecestat	AstraZeneca	BACE 1 inhibitor	43
CAD106	Novartis	Amyloid beta vaccine	29
Gantenerumab	Roche	Amyloid beta MAb	14
AMG 520	Amgen/Novartis	BACE 1 inhibitor	13

Place your bets

News of aducanumab being granted fast-track status came a day after it made global headlines as a result of the publication in *Nature* of full data from the phase Ib Prime trial. That study showed a statistically significant reduction in amyloid plaques in the brain in the three highest doses, 3mg/kg, 6mg/kg and 10mg/kg, at 26 weeks, a sign that it could help to slow progress of the degenerative disease.

However, as previously disclosed last year, on one of two clinical efficacy measures, the Mini-Mental State

Examination, the 1mg and 6mg doses missed significance while the 3mg and 10mg achieved it, raising questions about dose response (*Glimmers of support, but no Alzheimer's breakthrough, July 23, 2015*).

And the antibody, which like solanezumab, gantenerumab and crenezumab binds to amyoid beta in the hope of preventing plaques, has also been linked to signs of brain oedemas, which were more pronounced in patients who are ApoE4 carriers, who have an elevated risk of Alzheimer's.

Nevertheless, Alzheimer's is a space in which hope is stronger than data in the popular imagination, and along with this there appears to be no shortage of investors prepared to back the amyloid-blocking approach, on which all but two of the late-stage candidates rely – including the BACE inhibitors verubecestat, lanabecestat and AMG 520.

Biogen shares rose 3% in early trading today after yesterday's post-market announcement of the FDA's action.

The knowledge that Lilly expects Expedition 3 to read out by the end of the year will not hurt this momentum. The Clinical Trials in Alzheimer's disease conference on December 8-10 has been speculated as a setting for release of these data.

In short, all of the elements are in place for another mini-bubble in Alzheimer's, as happened in the lead-up to last summer's release of aducanumab phase I data and additional analyses from earlier solanezumab trials. Investors have three months to ride this wave. Given the history of drug development here, it will take a cool head to hold on through the Expedition 3 results.

Study	**Project**	**Trial ID**
Expedition 3	Solanezumab	NCT01900665
Engage	Aducanumab	NCT02477800
Emerge	Aducanumab	NCT02484547

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