Evaluate Vantage

February 15, 2017

Verubecestat halt fails to stop the Bace chase

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Yet another chink has appeared in the amyloid hypothesis of Alzheimer's with Merck's discontinuation of a study of its Bace inhibitor verubecestat. But, with the company soldiering on, it seems that only a failure in very early-stage disease will finally kill off the theory.

The Epoch trial, in mild to moderate Alzheimer's, was stopped for futility, but the Apecs study of verubecestat in a pre-Alzheimer's population will continue. After numerous other setbacks, companies have moved towards treating ever earlier patient populations – and with data only on the distant horizon the amyloid hypothesis will remain hotly debated for some time (see tables below).

The Apecs trial results are not due for another two years, with other early-stage studies even further out. One red flag for Merck investors is Lilly's recent termination of a trial of its beta-amyloid antibody solanezumab in prodromal disease, patients with mild cognitive impairment (MCI) that can, but does not always, lead to Alzheimer's.

Lilly pointed to an overlap of patient populations in the Expedition Pro and its failed Expedition 3 study – an issue of recruitment that could also affect Merck's Apecs study.

However, it is difficult to compare the two trial patient populations directly. Expedition Pro enrolled those with a Montreal Cognitive Assessment score of 17-28; those with MCI have an average score of around 22, falling to around 16 in Alzheimer's patients. The Apecs Clinicaltrials.gov listing does not give a similar score in its inclusion criteria, only saying that enrolees will have had a history of subjective memory decline.

Either way, Merck's investors did not seem too perturbed by the development, with its stock opening down around 1% this morning, reflecting the fact that many had already assumed that the Epoch study would fail.

Even earlier?

Beta-amyloid antibodies and Bace inhibitors are both designed to reduce amyloid levels in the brain, the former by clearing it and the latter by preventing its production. But so far they have failed to show an impact on Alzheimer's symptoms.

If the amyloid hypothesis is valid – which is now even more questionable – the next logical step would be treating people who have not yet developed Alzheimer's, before amyloid levels become critical. Many companies are already looking into this with Bace inhibitors and amyloid antibodies.

Selected Bace inhibitors in clinical development					
Product	**Company**	**Phase**	**Trial**	**ID**	**Primary completion**
Verubecestat (MK-8931)	Merck & Co	III	Apecs; prodromal AD	NCT01953601	Feb 2019
Lanabecestat	AstraZeneca/ Lilly	III	Daybreak-Alz; mild AD Amaranth; early AD	NCT02783573 NCT02245737	Aug 2019 for both
Elenbecestat (E2609)	Eisai/Biogen	III	MissionAD1; early AD MissionAD2; early AD	NCT02956486 NCT03036280	Jun 2020 Aug 2020
JNJ-54861911	Johnson & Johnson/Shionogi	II/III	Early; at-risk population	NCT02569398	Apr 2023
LY3202626	Lilly	II	Navigate-AD; mild AD	NCT02791191	May 2019
CNP520	Novartis/ Amgen	II	Generation; at-risk population	NCT02565511	Aug 2023
Source: EvaluatePharma.					

Lilly is already studying sola in the A4 study in older people at risk of Alzheimer's, defined as those with evidence of amyloid plaques detected by PET imaging. However, even if this strategy succeeds, implementing and paying for it in real life would likely be prohibitive.

And there are those who believe that sola failed not just because of treating patients too late, but also owing to drawbacks with the molecule itself. It binds soluble beta amyloid monomers so is thought only to slow the rate of new plaque formation; meanwhile, other MAbs like Biogen's aducanumab and Roche's crenezumab are thought to remove insoluble – or deposited – plaques from patients' brains.

Leerink analysts are predictably bullish about aducanumab and crenezumab's chances in spite of the Epoch halt – pointing to the earlier-stage population being studied, a different primary endpoint and the use of PET imaging at baseline to confirm the presence of amyloid – this was not done in Epoch.

Meanwhile, Novartis and Amgen are going even earlier, claiming to have the only programme focused on a genetically identified pre-Alzheimer's population, which is being treated with their Bace inhibitor CNP520.

Although many cling on to the fact that the amyloid hypothesis has not been definitively disproven, this latest blow is hardly encouraging for these remaining assets. Barring any other early abandonments the next test is still two years away, with Merck's second shot with verubecestat.

Selected early stage studies of beta-amyloid antibodies			
Project	**Study**	**Trial ID**	**Primary completion**
Solanezumab	Expedition Pro; prodromal AD	NCT02760602	Stopped
	DIAN2; dominantly inherited AD	NCT01760005	Sep 2019
	A4; preclinical AD	NCT02008357	Oct 2020
Aducanumab	Engage; early AD	NCT02477800	Nov 2019
	Emerge; early AD	NCT02484547	Feb 2020
Crenezumab	Cread; prodromal to mild AD	NCT02670083	Aug 2020
Source: EvaluatePharma.			

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