Evaluate Vantage

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Lilly boosts biopharma with an early Alzheimer’s signal

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Donanemab’s apparent success in a mid-stage trial can be read as support for the beta-amyloid hypothesis, but the reality is more complex.

Ask any investor what events might boost biopharma, and success in Alzheimer’s disease is typically near the top of the list. That Lilly should provide such news as all eyes are on the sector's JP Morgan Healthcare Conference is icing on the cake: the big pharma company’s shares soared 12% in early trade today, adding $19bn to Lilly’s valuation and sending other healthcare stocks higher.

An apparent success in the Trailblazer-Alz study of donanemab provided the trigger for this exuberance, with the antibody seeming to slow patients’ decline on functional and cognitive measures. However, a number of important issues should be borne in mind here, most notably the fact that the trial recruited only 272 patients. With a hit on the primary endpoint, however, investors seem happy to ignore this and other caveats for now.

The placebo-controlled phase II trial used iARDS for the primary endpoint, a composite assessment that combines two cognitive and functional measures, respectively known as ADAS-Cog13 and ADCSiADL. Donanemab slowed decline on iARDS by 32% relative to subjects in the control arm. The result was said to be statistically significant, although Lilly did not reveal the p value.

The company is also keeping secondary endpoints under wraps, although it said not all of these hit significance. These include several important measures that split out cognitive and functional scores, as well as biomarker analyses, cuts of the data that could easily shift the clinical relevance of the topline finding.

Thus the full presentation of these data at a conference later this year will be keenly awaited, as will results from a second trial of donanemab, Trailblazer-Alz2. This is double the size of Trailblazer-Alz and as primary endpoint uses CDR-SB, a better-known scale that more specifically tracks dementia development. Readout is unlikely to emerge before 2022, and regulators will surely want to see today’s signal confirmed before considering donanemab's approval.

Ones to watch in Lilly's Alzheimer's pipeline					
Product	**Mechanism**	**Status**	**Trial name**	**Alzheimer's setting**	**Data?**
Donanemab	N3pG-Ab MAb	Phase 2	Trailblazer-Alz	Early symptomatic	Hit primary endpoint Jan 2021
		Phase 2	Trailblazer-Alz 2	Early symptomatic	Still recruiting, primary completion Mar 2023
Zagotenemab	Tau deposit antibody	Phase 2	NCT03518073	Early symptomatic	Data expected late 2021
LY3372993	N3pG-Ab MAb	Phase 1	NCT04451408	Mild cognitive impairment due to AD	Primary completion Feb 2022
Source: clinicaltrials.gov, company releases.					

What makes the Trailblazer trials interesting is that biomarkers were used to select patients very specifically, a strategy that some believed would boost the chances of a signal being seen. The presence of amyloid plaques and Tau was confirmed by brain scan and measured at the start and end of the trials; Trailblazer-Alz specified that patients should have low to medium levels of Tau, while Alz2 stratifies for patients with high levels of Tau.

Lilly has long argued that donanemab's unique mechanism allows for swift and efficient clearance of the plaques thought to cause the damage in Alzheimer's. And one further piece of information the company released today seems to support this: donanemab-treated patients, on average, showed an 84 centiloid reduction of amyloid plaque at 76 weeks compared to a baseline of 108 centiloids.

Less than 25 centiloids is typical of a negative amyloid scan, so the link that Lilly is trying to draw here is that clearing those plaques has read through to cognitive and functional endpoints. However, ahead of full data from this trial – and with the beta-amyloid hypothesis still the subject of much debate – many will want to see a lot more on donanemab before coming to this conclusion.

Of course the company with most at stake here is Biogen, and its executives speaking at the JP Morgan conference today claimed that Lilly's result did indeed "reinforce" the beta-amyloid hypothesis. A 3% jump in Biogen shares suggests that some investors agree.

Still, an important distinction between donanemab and Biogen's aducanumab is that the former targets a modified form of beta amyloid called N3pG. Various forms of beta amyloid are known to exist, and some are thought to be more toxic, although again the relevance of this distinct mechanism has yet to be confirmed, certainly versus the influence of trial design in the case of Trailblazer-Alz.

Another important piece of missing information from Lilly concerns immunogenicity; donanemab is known to be strongly immunogenic and Lilly already has a follow-on project, LY3372993, in early trials. Again, this suggests that it will be some years before the full potential of targeting N3pG-Ab is revealed. However, as a first step these results certainly feel like they are going in the right direction, which for the Alzheimer's world is praise indeed.