Evaluate Vantage

February 10, 2020

Another Alzheimer’s failure for Biogen bulls to shrug off

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A fresh blow to the beta-amyloid hypothesis has not rattled Biogen's supporters, but Lilly shareholders were apparently hoping for more.

Wonder whether Biogen’s resurrection of aducanumab has stoked unrealistic hopes for Alzheimer’s disease progress? Look no further than Lilly’s shares, which opened 4% down this morning on the failure of the Dian-Tu study, an ambitious trial handicapped by a very small sample size.

Biogen shares were largely unmoved, meanwhile; while a positive signal in Dian-Tu would have been claimed as a major endorsement of the beta-amyloid hypothesis, aducanumab bulls have swiftly pointed to trial design and differences in the antibodies involved. These might be valid points, but yet another setback for this space only emphasises just how precarious Biogen’s position is here.

Dian-Tu was run by Washington University, and tested two failed anti-amyloid beta antibodies, Lilly’s solanezumab and Roche’s gantenerumab, in subjects with a rare inherited form of early-onset dementia called autosomal-dominant Alzheimer's disease (ADAD). Because these individuals display degeneration at a predictable age, researchers hoped to tease out a benefit in a small number of subjects (A*nother chance for Lilly and Roche to take on Alzheimer's, January 31, 2020*).

None was seen, at least according to the primary endpoint of the study: neither project showed a significant slowing of cognitive decline, statements from Lilly and Roche said today. These press releases also confirmed the very small number of patients that received the active agents; 52 were randomised to receive gantenerumab, while only 50 received solanezumab.

The full data, due to be presented at a medical conference in April, remain of interest. The high doses tested in Dian-Tu helped rekindle hopes here, echoing Biogen’s case for finding a way forward for aducanumab: that if you dose patients high enough and long enough, an effect can be seen. But Dian-Tu only hiked the dosages half way through; this, and the very small sample size, will surely render any positive signals to emerge in the full results exploratory at best.

Important differences? How the amyloid-beta antibodies differ, mechanistically			
	Aducanumab	**Gantenerumab**	**Solanezumab**
Target	Fibrillar and oligomeric amyloid-beta	Fibrillar and oligomeric amyloid-beta	Soluble monomeric amyloid-beta
Epitope	N-terminus (3-7)	N-terminus (3-11) and mid-domain (18-27)	Mid-domain (16-26)
Plaque binding	Yes	Yes	No
Source: sellside research.			

Analysts at SVB Leerink, who only a few weeks ago declared that the Dian-Tu outcome would influence whether confidence in beta-amyloid as a target, and thus Biogen's antibodies, went up or down, today decided that the outcome had limited impact on aducanumab. The bank has been a major supporter of Biogen's stance that aducanumab is approvable.

These three anti-beta-amyloid antibodies all work slightly differently, targeting different epitopes, Leerink pointed out. Again, the small number of patients involved here surely means that mechanistic conclusions are hard to draw.

Still, it is hard to escape the notion that Biogen's putative progress with aducanumab raised unrealistic hopes here. The next big test for this mechanism will probably come from Roche's gantenerumab, which is due to complete a prodromal study later this year, and Biogen bulls will no doubt be ready with reasons should this fail too.

Selected upcoming Alzheimer's disease readouts					
Company	**Project**	**Mechanism**	**Trial**	**Setting**	**Estimated timing**
Roche	gantenerumab	Anti-beta-amyloid MAb	NCT01224106	Prodromal (phase III)	Mid-2020
Roche/AC Immune	Semorinemab (RG6100)	Anti-Tau MAb	NCT03289143	Prodromal/Mild AD (phase II)	Mid-2020
Biohaven	troriluzole	Glutamate modulator	NCT03605667	Mild-to-moderate AD (phase II/III	Late 2020
Eli Lilly	Donanemab (LY3002813)	N3PG antibody	Trailblazer-Alz NCT03367403	Early symptomatic AD (phase II)	Late 2020
Cortexyme	COR388	Gingipain inhibitor	Gain NCT03823404	Mild to moderate AD (phase II/III)	Poss interim analysis mid/late 2020; completion late 2021.
Abbvie	ABBV-8E12	Anti-Tau MAb	NCT02880956	Early AD (phase II)	2020 (primary completion Apr 2021)
Roche	gantenerumab	Anti-beta-amyloid MAb	NCT02051608	Mild AD (phase III)	Q2 2021
Biogen	Gosuranemab (BIIB-092)	Anti-Tau MAb	Tango NCT03352557	Early AD (phase II)	2021
Lilly	Zagotenemab (LY3303560)	Anti-Tau MAb	NCT03518073	Early symptomatic AD (phase II)	2021
Source: EvaluatePharma & company statements.					