Evaluate Vantage

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Shock revelation sees Biogen erase its aducanumab losses

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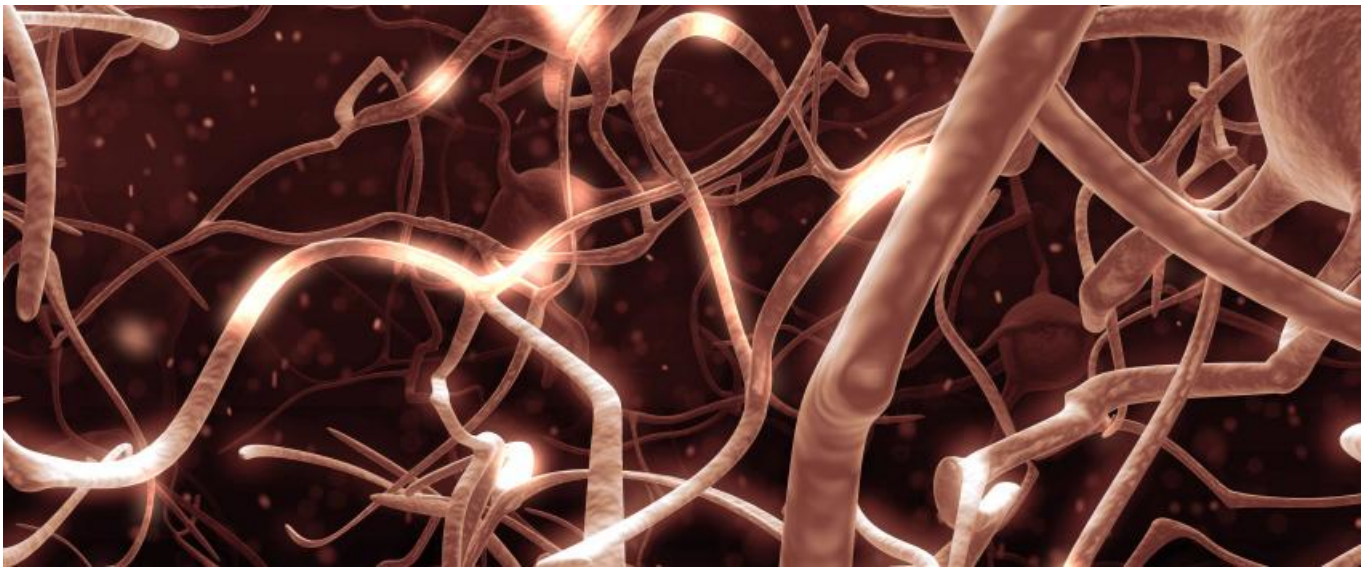

The amyloid-beta project is to be filed for Alzheimer's, and Biogen's market cap regains the $15bn it lost in March.

After numerous setbacks Biogen needed to make a decisive move to restore investor confidence, but few were expecting this. The company is to file its ill-fated amyloid-beta MAb aducanumab for US approval.

The last time investors had heard of this asset was in March, when Biogen was scrapping it after the failure of both its pivotal studies, Emerge and Engage, at interim analysis. Today the group spelled out the extent of the machinations that have gone on behind the scenes since March, and sensationally revealed: "In retrospect the result of our futility analysis was incorrect."

Biogen said that, far from throwing in the towel on aducanumab, it has been busy. A "type C" meeting with the US FDA took place in June to discuss a possible path forward; then, just yesterday, there was a second such meeting, at which a new analysis was discussed, resulting in today's announcement that aducanumab would be filed next year.

The crux of the matter is that a new, longer-term analysis of the two pivotal trials has been carried out, the result of which is an allegedly positive hit in Emerge and supportive data from a still negative Engage study. Crucially, Biogen claims that its interactions with the FDA suggest that this outcome supports filing.

High enough for long enough

While the issues are complex the group's new analysis points to a single, simple fact, which has been aired before: if an amyloid-beta MAb can be dosed high enough, for long enough, without insurmountable toxicities, then it should show some effect in a sufficiently early Alzheimer's population.

But the way Emerge and Engage were analysed was in hindsight incorrect, Biogen claims. The futility assessment of the pooled data only took into account subjects who had completed 18 months' treatment at December 2018.

This was correct according to the statistical plan, but in hindsight missed the fact that with longer-term follow-up the effect of the highest, 10mg/kg, aducanumab dose would push Emerge to a positive readout. "At the time of the futility analysis Emerge was trending positive, while Engage was not," Biogen said today. "We did not understand the drivers of these different results."

If this logic holds water, then it appears that two protocol amendments scuppered the futility analysis. The first, in July 2016, concerned subjects in whom dosing had been suspended owing to the side effect of vasogenic oedema (ARIA-E); these were allowed to resume on aducanumab at their originally assigned dose.

The second, in March 2017, allowed ApoE4 carriers who had earlier been on either 6mg/kg or 10mg/kg to be titrated up to 10mg/kg. This saw more patients overall exposed to 10mg/kg, but crucially the December 2018 cutoff was too early for this effect to manifest itself.

Accordingly, only with the longer follow-up does it become evident that Emerge shows the nominally positive effect of the 10mg/kg dose on the primary endpoint, a dementia rating scale called CDR-SB. This effect is not seen in Engage, though the low doses in both trials perversely show a similar effect on CDR-SB. Full data are to be presented at CTAD in December.

Surprise! Biogen's longer-term analysis of aducanumab				
	Low dose		**High dose**	
	Emerge	Engage	Emerge	Engage
	n=543	n=547	n=547	n=555
CDR-SB (original primary endpoint)				
Reduction vs placebo	-14%	-12%	-23%	+2%
Nominal p value	0.117	0.236	0.010	0.825
Adas-Cog (one of 3 secondary endpoints)				
Reduction vs placebo	-14%	-11%	-27%	-12%
Nominal p value	0.167	0.248	0.010	0.245
Source: Biogen presentation.				

As well as the statistical rigour of this analysis, any US advisory committee is likely also to focus on aducanumab's toxicity profile.

Biogen said ARIA-E was the most common adverse event across the two studies, manifesting in 35% of the studies' subjects. However, three quarters of patients with ARIA-E did not experience symptoms, and the oedema episodes resolved in 4-16 weeks, "typically without long-term clinical sequelae".

Investors today traded Biogen up 35%, putting its market cap at $56bn, nearly where it was before the results of the futility analysis were revealed in March. They will also now pay attention to the company's second amyloid-beta MAb, BAN2401, which despite flunking phase II was this year pushed into a 1,500-subject pivotal trial.

For now Biogen has seen enough to hail aducanumab as the first therapy to reduce clinical decline in Alzheimer's. Today its chief executive, Michel Vounatsos, said drug development was rarely straightforward. Should aducanumab's rollercoaster ride end with US approval that could turn out to be the understatement of the year.