Evaluate Vantage

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Gantenerumab fails to Graduate

Elizabeth Cairns

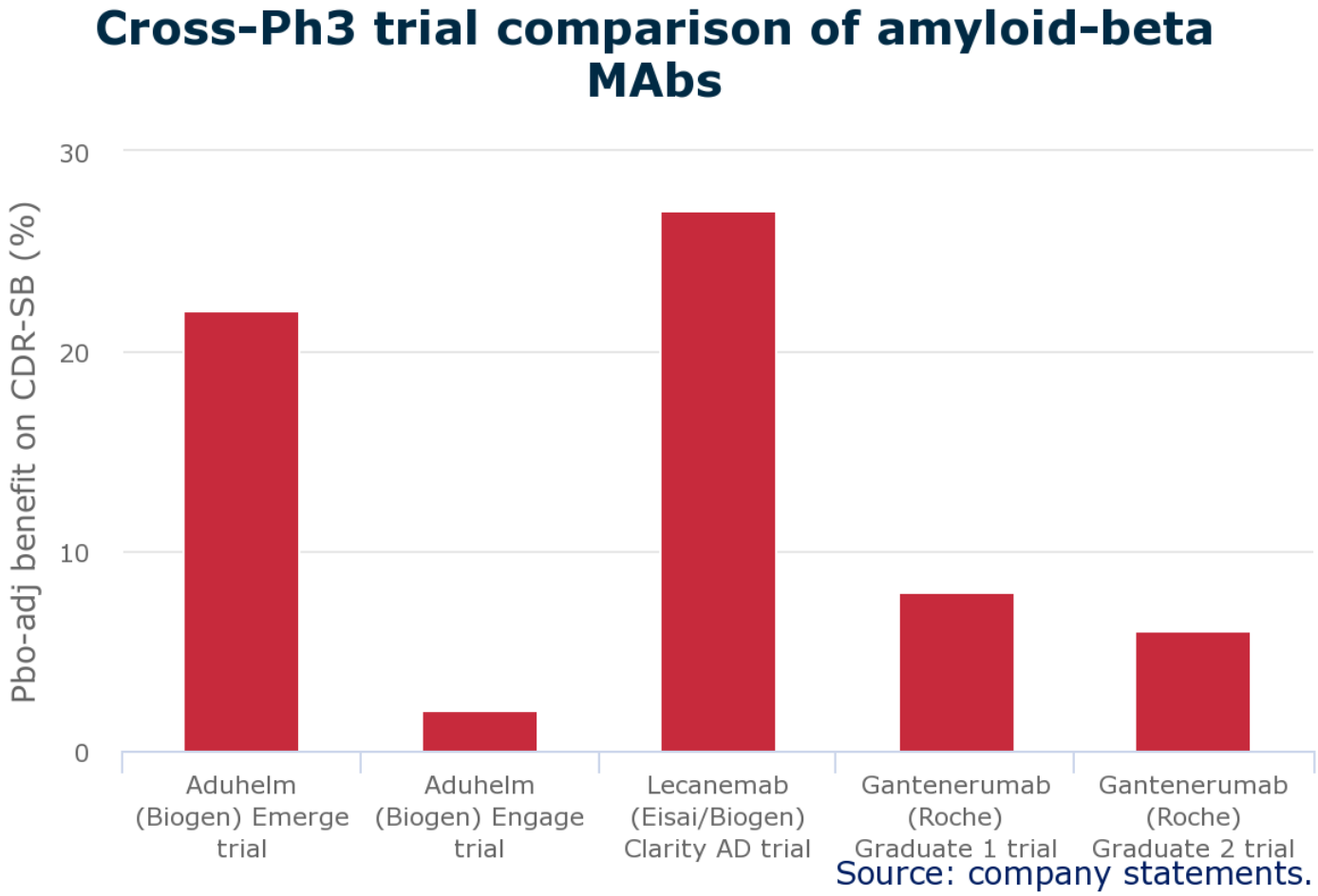
Roche’s Alzheimer’s antibody looks likely to join the scrapheap. But the company is determined to keep plugging away at the disease.

Last month Roche said that if one of the two pivotal Graduate trials hit, it would file gantenerumab for Alzheimer’s disease using pooled data. That strategy seems unlikely to help: today the group disclosed that both trials failed.

Roche has stopped short of stating that gantenerumab is dead, instead emphasising the other Alzheimer’s candidates in its pipeline. Two of these, including a formulation of gantenerumab using a novel delivery technology, also target amyloid – perhaps explaining why Roche blamed the Graduate fails on lower-than-expected levels of beta-amyloid clearance.

In Graduate 1 and 2, gantenerumab slowed clinical decline, as measured by the clinical dementia rating-sum of boxes (CDR-SB), by -0.31 and -0.19 from baseline score at 116 weeks. These represented relative reductions versus placebo of just 8% and 6% respectively, and neither was statistically significant.

These are well below the -0.45, or 27% placebo-adjusted, reduction seen with Biogen/Eisai’s lecanemab in Clarity AD two months ago. Even one of Aduhelm’s twin pivotals, Emerge, beat this showing on CDR-SB.



Note: Only Emerge and Clarity AD data reached statistical significance. Emerge, Engage and Clarity AD data at 78wk, Graduate 1 and 2 data at 116wk.

On safety, amyloid-related imaging abnormalities with oedema or effusion (Aria-E) occurred in 25% of pooled gantenerumab-treated patients, with Roche saying that the “vast majority” were asymptomatic, and that very few cases led to treatment discontinuation.

More detailed findings from Graduate 1 and 2, as well as those from Clarity-AD, are due at the Clinical Trials on Alzheimer’s Disease (CTAD) meeting at the end of this month.

The other candidate in this space is Lilly’s donanemab, which hit in phase 2 nearly two years ago. This used a different measure, iARDS, as the primary outcome, so comparisons are hard. Donanemab is now in a suite of phase 3 trials, including Trailblazer-Alz 4, head-to-head versus Aduhelm, which Lilly recently said had hit.

Keeping faith

In ascribing the Graduate failures to gantenerumab's removal of less beta-amyloid than had been expected, Roche seems to be attempting to keep the amyloid hypotheses, battered over recent years despite lecanemab’s success, alive.

Roche’s faith in the amyloid theory is underscored by the fact that it has two other anti-amyloid MAbs in the clinic. Most advanced is a version of gantenerumab bound to Roche’s brain shuttle technology, designed to increase penetration of large molecules into the brain.

This is in Brainshuttle AD, a phase 1/2 trial in prodromal or mild to moderate disease. The agent will be dosed monthly via intravenous infusion, and data could come towards the end of 2024.

The other, crenezumab, also looks unlikely to reach the market. This failed in pivotal studies three years ago, and an attempt to steer it towards a subgroup with the E280A mutation, the most common cause of familial early-onset Alzheimer’s, misfired this summer. It does not seem to be in any active trials.

The two further pipeline projects take aim at a different, though also disputed, pathway: tau. Again, one – semorinemab – looks somewhat like an also-ran, failing one phase 2 trial and posting mixed data in another. Perhaps bepranemab, licensed from UCB in 2020, can do better when its phase 2 study in mild disease reads out in a couple of years or so.

Until bepranemab and the new form of gantenerumab yield their mid-stage data, Roche investors have little to

hope for in Alzheimer’s. The company's stock sank 4% today, while Biogen climbed 5%.

Roche's Alzheimer's pipeline		
Project	**Mechanism**	**Status**
RG1450 (gantenerumab)	Anti-beta-amyloid MAb, licensed from Morphosys	Ph3 Graduate 1 and Graduate 2 trials failed Nov 2022
RG6102 (brain shuttle gantenerumab)	Anti-beta-amyloid MAb bound to "brain shuttle" tech, intended to aid BBB penetration	In Ph1/2 trial in prodromal or mild-to-moderate Alz, data poss 2024
RG7412 (crenezumab)	Anti-beta-amyloid MAb, partnered with AC Immune	Pivotal Ph3 Cread and Cread 2 trials failed Jan 2019 Ph2 trial in pts w presenilin1 E280A mutation failed Jun 2022
RG6416 (bepranemab)	Anti-tau MAb, partnered with UCB Biopharma	In Ph2 in mild cognitive impairment or mild Alz, data poss 2024
RG6100 (semorinemab)	Anti-tau MAb, partnered with AC Immune	Failed Ph2 Tauriel in prodromal/mild Alz Sep 2020 Met one co-primary in ph2 Lauriet in mild/moderate Alz Aug 2021
RG6289	Undisclosed	In Ph1 according to pipeline
Source: Evaluate Pharma, clinicaltrials.gov		

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Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754

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