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Why not bapineuzumab?

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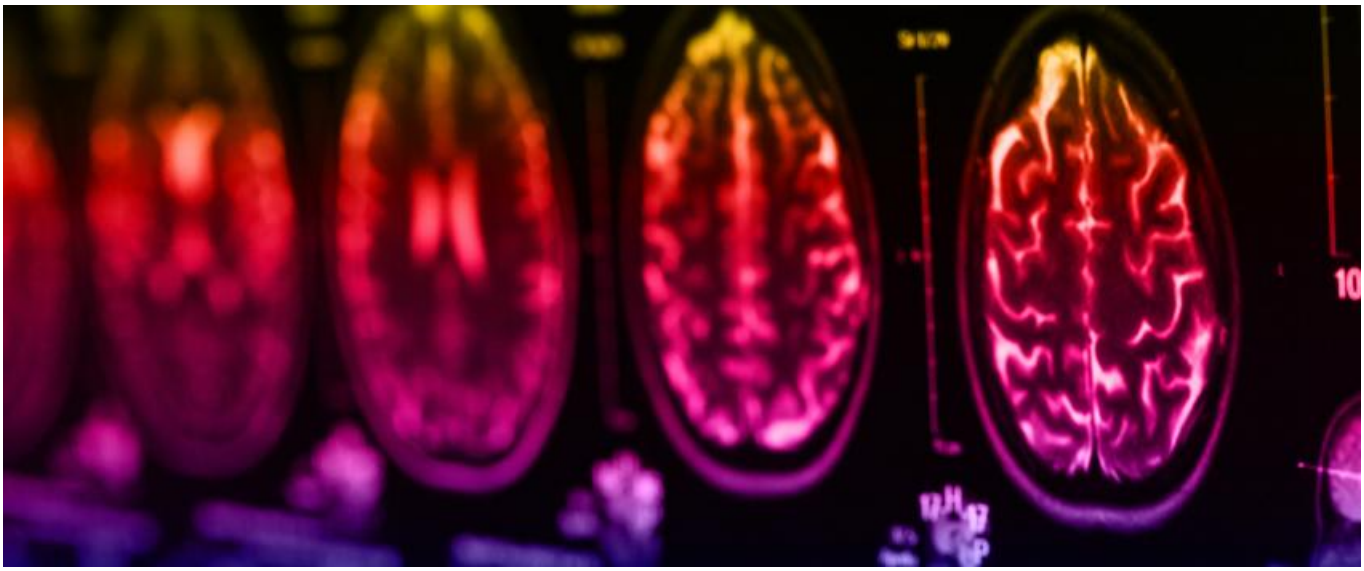

Like Aduhelm this long-discontinued amyloid beta MAb reduced brain beta amyloid; so have several other industry projects.

The US FDA justified yesterday's accelerated US approval of Biogen's Aduhelm by citing evidence of the drug reducing amyloid beta plaque in the brain. This controversial move should have several other companies hastily looking at failed studies of their own amyloid-beta MAbs for signs of activity on this novel surrogate endpoint.

For instance, should Pfizer/Johnson & Johnson now resurrect bapineuzumab, canned in 2012 after flunking several phase 3 studies? A trawl of published data shows that, indeed, bapi did show an effect on brain amyloid burden, which in one large trial hit nominal statistical significance versus placebo.

A second trial also showed a numerical difference versus placebo, though this came in at p=0.159. The remaining two phase 3 tests showed no effect, according to results published in NEJM, though they did demonstrate strong increases in plasma amyloid beta versus placebo, suggesting that at least some amyloid was being cleared from the brain.

Biomarker expedition

Lilly's solanezumab also prompted rises in plasma amyloid beta between 12 and 80 weeks, and the Expedition and Expedition-2 trials showed nominal statistical significance versus placebo in reducing amyloid beta in the cerebrospinal fluid. Expedition-3, however, showed no effect on pre-existing amyloid plaques.

Rather than resurrecting solanezumab, Lilly should perhaps now focus on donanemab, which has already shown impressive effects on this biomarker. However, this was in a relatively small study, and the company has started a phase 3 programme.

Though a snap decision to file a failed project like bapi or sola might seem facetious, it is a situation of the FDA's own making if its endorsement of a mechanistic biomarker opens the floodgates. Enthusiasm should perhaps be tempered by the view that any asset following in Aduhelm's footsteps would not be truly novel and might thus not get the same regulatory support.

Still, the fact remains that many amyloid beta-targeting projects do do what they say on the tin. Only Roche's crenezumab appears to lack evidence of brain amyloid beta activity, but this is through lack of published data after its Cread and Cread-2 studies were hastily scrapped in 2019.

Even the Swiss group's gantenerumab has been shown to lower amyloid beta, albeit in open-label extensions

at high doses and not in its original phase 3 trials. One caveat is that different means of measuring this biomarker make direct comparison with the effect being claimed on Aduhelm's label difficult.

Selected studies of amyloid beta Mabs			
Trial	**Total recruitment**	**Population**	**Summary of effects on amyloid beta**
Bapineuzumab			
Study 3001	1,100	Mild-moderate ApoE4 carriers	-0.05 chg from baseline in SUVR by PIB-PET for 0.5mg/kg at 71wk, vs +0.02 for placebo (p=0.159)
Study 3000	901	Mild-moderate ApoE4 non-carriers	-0.01 chg from baseline in SUVR by PIB-PET for pooled doses at 71wk, vs +0.01 for placebo (p=0.654)
Study 302	1,121	Mild-moderate ApoE4 carriers	0.0 chg from baseline in brain amyloid burden by PIB-PET for 0.5mg/kg at 71wk, vs +0.1 for placebo (p=0.004)
Study 301	1,331	Mild-moderate ApoE4 non-carriers	No difference vs placebo in brain amyloid burden by PIB-PET for 0.5mg/kg or 1.0mg/kg at 71wk (p=0.19 & 0.47)
Solanezumab			
Expedition	1,000	Mild-moderate AD	-1,902.1pg/ml chg from baseline in total CSF Aβ40 at 80wk, vs +1,325.4pg/ml for placebo (p=0.002)
Expedition-2	1,040	Mild-moderate AD	-876.4pg/ml chg from baseline in total CSF Aβ40 at 80wk, vs +3,033.1pg/ml for placebo (p=0.001)
Expedition-3	2,129	Mild AD	No effect on preexisting amyloid plaques
Aduhelm			
Emerge	1,638	Early AD	-0.264 chg from baseline in Aβ PET composite SUVR for high dose at 78wk, vs +0.014 for placebo (p<0.0001)
Engage	1,647	Early AD	-0.235 chg from baseline in Aβ PET composite SUVR for high dose at 78wk, vs -0.003 for placebo (p<0.0001)
Prime (ph1)	197	Prodromal or mild AD	-0.263 chg from baseline in Aβ PET composite SUVR for 10mg/kg at 54wk, vs +0.014 for placebo (p<0.0001)
Gantenerumab			
Scarlet Road	799	Prodromal AD	Open-label extension at highest dose showed 58% & 50% of pts below Aβ positivity threshold at 1yr & 2yr, vs 37% at baseline
Marguerite Road	389	Mild AD	Open-label extension at highest dose showed 33% & 55% of pts below Aβ positivity threshold at 1yr & 2yr, vs 14% at baseline
Crenezumab			
Cread/BN29552	813	Prodromal-mild AD	Discontinued, no published data on Aβ levels
Cread-2	806	Prodromal-mild AD	Discontinued because of above trial
Donanemab			
Trailblazer-Alz (ph2)	266	Early symptomatic AD	-85.06 centiloid chg from baseline in amyloid plaque level at 76wk, vs +0.01 centiloids for placebo
SUVR=standard uptake value ratio; all studies ph3 except where indicated. Source: scientific publications.			

All eyes will now turn to the A4 study of sola in patients with memory loss, and Clarity AD, a trial of

Eisai/Biogen’s lecanemab in early Alzheimer’s, both possibly ending next year.

A final point relates to bapineuzumab’s key US patents, which start expiring this year, according to *Evaluate Pharma*. Though any company that launched this drug would benefit from several years’ data exclusivity, the lack of formal IP might interest health authorities troubled by Aduhelm’s $56,000 annual cost.

Recent years have seen at least two companies, EQRX and Coherus, founded with a mission to launch low-cost drugs. Wishful thinking? Watch this space.