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NEWS IN BRIEF

BACE inhibitor bust in Alzheimer trial

Merck & Co. has halted a pivotal trial of its β-secretase 1 (BACE1) inhibitor verubecestat in mild-to-moderate Alzheimer disease (AD) due to futility, providing a first critical failure for yet another class of amyloid-modulating drugs.

Trials have already sunk other classes aimed at controlling amyloid plaques, including γ-secretase inhibitors, which were designed to regulate a key step in amyloid processing, and anti-amyloid antibodies, which target amyloid directly. With these failures, several companies had turned their focus to BACE1 inhibitors, which act upstream of γ-secretase in amyloid processing.

One of the leading BACE1 inhibitors is Merck's verubecestat, with a phase II/III trial in more than 2,000 patients with mild-to-moderate AD that was expected to read out in mid-2017. The company instead halted the trial in February after an interim safety analysis found that there was "virtually no chance of finding a positive clinical effect".

Although the failure is yet another blow to the embattled amyloid hypothesis of AD, it could be due to various other factors, including insufficient potency or poor pharmacokinetics. A leading theory is that amyloid-modulating drugs need to be on board earlier in the course of the disease to delay neurodegeneration. To this end, Merck is still running a phase III trial of its verubecestat in patients with prodromal AD. Top-line results from this trial are anticipated in 2019.

Four other companies have BACE1 inhibitors in mid- or late-stage trials, in various patient populations, including asymptomatic patients at risk for AD (TABLE 1).

In another recent AD setback, Eli Lilly terminated the phase III trial of its anti-amyloid antibody solanezumab in prodromal AD patients. Late last year, the monoclonal antibody failed in patients with mild-to-moderate AD and evidence of amyloid accumulation in the brain (*Nat. Rev. Drug Discov.* **16**, 3–5; 2017).

Table 1 | **BACE1 inhibitors in mid- and late-stage trials**

Drug name	Company	Status	Patient population
Verubecestat	Merck & Co.	Phase III	Prodromal AD
Elenbecestat	Biogen/Eisai	Phase III	Early AD
AZD3293	AstraZeneca/Eli Lilly	Phase III	Early and mild AD
JNJ-54861911	Johnson & Johnson	Phase II/III	Asymptomatic at-risk patients (family history, APOE4 or biomarker positivity)
CNP520	Novartis	Phase II	Asymptomatic at-risk patients (APOE4)

AD, Alzheimer disease; APOE4, apolipoprotein E4; BACE1, β-secretase 1.

Asher Mullard

New plaque psoriasis approval carries suicide warning

The FDA approved Valeant's brodalumab for the treatment of moderate-to-severe plaque psoriasis, but with the warning that the drug is associated with suicidal ideation and behaviour.

The antibody targets the interleukin-17 (IL-17) pathway, fertile ground for drug developers. Although the drug follows on the heels of Novartis's secukinumab and Lilly's ixekizumab, which target IL-17 ligands, this is the first approval for a therapy that targets the IL-17 receptor (IL-17R). Because IL-17R binds to multiple ligands, its developers hoped that it would provide broader blockade against pathway activation and therefore benefits over the competition.

AstraZeneca and Amgen, who collaborated on the development of brodalumab, instead found a risky side effect profile. In clinical trials of the drug, 34 of 4,464 plaque psoriasis patients who received the drug experienced suicidal ideation.

The mechanistic explanation for an increased suicide risk is unknown, and other drugs that target the same pathway have not raised the same safety flag (*Nat. Biotechnol.* **33**, 894–895; 2015). Nevertheless, these findings prompted Amgen to drop its interest in the drug in 2015. Months later, AstraZeneca licensed brodalumab to Valeant for US$100 million up front, $345 million in possible milestones and a share of any profits.

The drug now enters a competitive field. In addition to the approved IL-17 monoclonal antibodies (mAbs), there is growing interest in anti-IL-23 mAbs that act upstream in this pathway. The agency approved Johnson & Johnson (J&J)'s IL-23- and IL-12-targeting mAb ustekinumab for psoriasis in 2009. Next-generation competitors that target only IL-23 — and so do not act on the T helper 1 cell immune response — may offer an improved safety profile. J&J's IL-23-specific candidate guselkumab is under review at the FDA, and Sun Pharmaceutical Industries' tildrakizumab and AbbVie's risankizumab are in phase III.

Asher Mullard

Biotech gender gap

Women hold only around 10% of the board positions in biotech firms, found a recent report on the biotech gender gap by Liftstream, a life sciences recruitment company.

This finding is based on an analysis of the boards of 177 biotech firms that filed to go public between 2012 and 2015. This mirrors the results of a related study from the same group that looked at 1,491 therapeutic and diagnostic companies and found that women held 11% of board seats in Europe and 10% of those seats in the United States. These counts are down from a 19% average stake across all industries, as reported by a broader analysis of Fortune 1000 companies.

The new study focused specifically on companies that are undergoing initial public offerings (IPOs), because it is a transformative stage in terms of financing, ownership and governance structures. As such, the authors of the report argue, it offers an "opportunity to refresh and reconstitute [the] boards". Although they found minor improvements in diversity immediately after an IPO, this trend was not sustained over time.

The report also makes a business case for the benefits of gender balance. It found that boards with both men and women experienced an average 19% increase in share price, whereas all-male boards experienced a 9% decrease in share price.

Given the slow pace of change, the authors estimate that it will take until 2036 for women to hold even 30% of biotech board positions. "This poor prognosis means there is a need for interventional approaches to accelerate the cadence of this change," they argue. Some such efforts are being trialled (*Nat. Med.* **23**, 141–143; 2017).

Asher Mullard