Another chance for Lilly and Roche to take on Alzheimer's

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The academic Dian-Tu study looks at anti-amyloid beta antibodies from Lilly and Roche; despite gantenerumab, hopes are being dialled back.

Alzheimer's disease is firmly back in focus thanks to Biogen, which last year stunned the field by eking a signal of efficacy from the pivotal programme of its abandoned amyloid beta project aducanumab. The disclosure has put the spotlight on another pending test of the amyloid beta hypothesis, the Dian-Tu trial, which is due to yield results in the coming weeks.

The study is being run by Washington University, and is testing two other failed anti-amyloid beta antibodies, Lilly's solanezumab and Roche's gantenerumab. Patients with a rare inherited form of early-onset dementia, autosomal-dominant Alzheimer's disease (ADAD), are being studied.

Carriers of the genes associated with ADAD are almost certain to display degeneration at a predictable age, which researchers believe creates a unique opportunity to test whether interventions can delay or slow the course of the disease.

Small

Around 490 presymptomatic patients were recruited for Dian-Tu; the relatively small number of subjects is one of the main reasons cited for low hopes of success, though the study designers argue that reliable disease progression models developed for ADAD should help detect changes in cognition with fewer patients – and improve the ability to detect drug effects.

Solanezumab and gantenerumab are both being pitted against placebo, with change in the Dian-Tu composite cognitive score as the primary endpoint, measured annually over four years. This composite score comprises four tests that the researchers believe are particularly suitable for patients in the very early stages of the disease.

Numerous secondary endpoints are being assessed, including biomarker information specific for each antibody. In the gantenerumab group brain scans will track deposits of amyloid-beta, while those in the solanezumab arm will assess amyloid-beta levels in cerebrospinal fluid. The hope here is that any hit on the primary endpoint will help validate the predictive power of these biomarkers.
As with all Alzheimer’s studies hopes of a clear success are low, though it is notable that Dian-Tu is testing very high doses of these agents and tracking patients for a long period. Biogen’s case for finding a way forward for aducanumab rests on exactly this hypothesis: that if you dose patients high enough and long enough, an effect can be seen.

**Molecule or hypothesis?**

Read-through to aducanumab will naturally be made, and, should Dian-Tu fail, Biogen seems ready to blame the projects being tested rather than the underlying hypothesis.

“If the results are positive, I think that that would lend further support to the amyloid hypothesis. If the results are negative, I’d want to see that there is evidence of target engagement and biological changes in the brain before I make any conclusions,” Al Sandrock, Biogen’s head of R&D, said on an investor call yesterday.

Roche and Lilly have both substantially dialled down development of gantenerumab and solanezumab; on Roche’s annual results call yesterday the Dian-Tu trial was not even raised. At Lilly’s presentation executives talked down expectations, with chief science officer Dan Skovronsky highlighting the small number of subjects and aggressive nature of this form of Alzheimer’s.

Still, at JP Morgan Lilly’s chief executive, Dave Ricks, remarkably suggested that solanezumab could be filed on positive Dian-Tu data. What the FDA makes of aducanumab has yet to be revealed, of course – Biogen was vague yesterday on when it might be submitted – but it seems likely that agency staff will also be awaiting the Dian-Tu results with interest.