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Interview – Probiodrug hopes to avoid Alzheimer's amyloid abyss

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The amyloid hypothesis of Alzheimer's disease seems almost invincible. Knock one company in the field down and another springs up to take its place. But Germany's Probiodrug is – like many before it – confident that it can succeed.

Probiodrug believes that not jumping straight to phase III from phase I, as some Alzheimer's players have done, will stand it in good stead. The group even dares to hope for conditional approval of its lead candidate, PQ912, based on data from phase IIb trials that are due to start this year.

Its chief development officer, Inge Lues, points to draft guidelines from the US FDA and new guidance from the European Medicines Agency, both released in February. These emphasise the treatment of early-stage patients and the importance of biomarkers, and could make it easier for Alzheimer's agents to get approved.

Rage fail

Still, the apparent flexibility of the agencies has not helped Alzheimer's drug development so far, and the woeful track record continued last week with the failure of VTV Therapeutics' Rage inhibitor azeliragon (*VTV pivots to diabetes after Alzheimer's flop, April 10, 2018*).

Rage lies upstream of three key Alzheimer's targets – amyloid-beta, Tau and inflammation – so the setback was another blow to the amyloid hypothesis.

Probiodrug's PQ912 also targets amyloid, but in a different way to candidates that have come before it, including Lilly's failed anti-beta amyloid MAb solanezumab. PQ912 is a small-molecule inhibitor of glutaminyl cyclase, the enzyme that converts beta amyloid into what Probiodrug calls the toxic pGlu-Abeta form.

Lilly's LY3002813 also aims to decrease the amount of pGlu-Abeta but, instead of hitting the enzyme, is a monoclonal antibody to this target. Probiodrug had previously told *EP Vantage* that its approach could be validated by a phase I trial of LY3002813, for which interim data were reported in June 2016; however, full analysis seems unlikely to be revealed (*Interview – Probiodrug pins hopes on Lilly readout, August 5, 2015*).

"They're still running their phase Ib," says Ms Lues. "In phase Ia they clearly indicated that they have very robust reduction in plaque load, more than 40-45% with the highest dose, 10mg." But she adds that because of the backbone of the antibody, LY3002813 is highly immunogenic, so is quickly cleared out of the system, "and you have to increase the dose. And they're obviously still working on that."

Looking for gems

PQ912, meanwhile, already has a phase IIa trial under its belt. Saphir, presented at last year's Clinical Trials on Alzheimer's Disease (CTAD) conference, primarily assessed safety, but it also looked at exploratory efficacy endpoints including cognitive tests, EEG measurements and cerebrospinal fluid (CSF) biomarkers – and Probiodrug believes that the signs were promising.

However, the trial did find a higher discontinuation rate in the treatment arm, with more skin and gastrointestinal adverse events seen with PQ912. Ms Lues pointed to the very high dose used, 800mg twice daily, which she says was selected deliberately to get very high levels of enzyme inhibition.

"Because of the huge target engagement we can safely reduce the dose in the next study," adds Professor Philip Scheltens, director of the Alzheimer Center at the VU University Medical Center in Amsterdam and the lead investigator of the Saphir study.

The planned 250-patient European phase IIb trial, Saphir 2, will start with a 150mg dose and titrate up to 300mg over the first 12 weeks, which will look at safety. "If we have no safety signals we'll continue," says Professor Scheltens.

The second stage will see the dose increased to up to 600mg. In total, patients in Saphir 2 will be treated for

around a year on average, versus Saphir's three-month duration.

Like Saphir, Saphir 2 will enrol people with either mild Alzheimer's disease or normal cognition – incorporating those with a mini mental state examination score of 21-30 – but with amyloid and Tau pathology, measured using CSF analysis or PET imaging, Professor Scheltens says.

The primary endpoint will be the neuropsychological test battery, which was an exploratory endpoint in Saphir.

Details of the US trial are less clear, but this is likely to be bigger, with around 400 patients, Ms Lues says. Edison analysts wrote that the US study would be "substantially similar in regard to patent population and titration", but added that the treatment period would be 18 months.

Amyloid agony

Professor Scheltens is not fazed by earlier Alzheimer's setbacks, saying: "Solanezumab just wasn't a good enough drug, and also the dose was much too low. [With Roche's] gantenerumab the dose was far too low."

He still believes in the amyloid hypothesis, saying: "It hasn't really been tested to its full truth. I don't think we've done the right trials with the right drugs and the right dose." But he acknowledges that repeated failures with amyloid-targeting projects have made it difficult to justify continuing with this approach.

He seems unsure of the prospects of the next big Alzheimer's hope, Biogen's aducanumab. "Aducanumab is very promising; it has very good phase I data with strong plaque reduction. But my personal advice would have been to go for phase II first before jumping into phase III."

Probiodrug believes that it has addressed this with a more cautious approach with PQ912. But, with results from Saphir 2 not due for a couple of years, be prepared for more blows to the amyloid hypothesis in the meantime.

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