Evaluate Vantage

January 30, 2019

Crenezumab flop makes Biogen bulls a little more nervous

Jacob Plieth

One day after Biogen expands aducanumab trials, a canary in the coal mine, the rival crenezumab, fails in phase III.

If today's failure of Roche/AC Immune's crenezumab was, in hindsight, predictable, this will come as little solace to Biogen investors. Crenezumab's phase III readout had been seen as an indicator of the chances of success of Biogen's most important near-term driver, its own phase III amyloid-beta MAb aducanumab.

Investors still holding out for aducanumab might be feeling especially nervous given that Biogen yesterday seemed to double down on the project. For Roche and AC the crenezumab setback will be disappointing given the design work that had gone in to maximising the project's chances of success.

Two years ago AC had spelled out how crenezumab, an antibody of the IgG4 isotype, was able to clear the brain without causing inflammation. This should have minimised its chances of causing the ARIA-E side effect – a fact borne out in earlier trials – and enabled high enough dosing to have a chance of showing efficacy.

Today, however, it became apparent that this had not panned out. Roche said it was discontinuing crenezumab's two pivotal trials, Cread 1 and 2, after an interim analysis suggested that their primary endpoint, change in CDR-SB score, was unlikely to be hit.

While Roche stock was unmoved, AC's crashed 65% in early trade on Nasdaq. And the read-across to Biogen was evident, with that company's shares opening down 3%.

Just yesterday Biogen said it was starting a new phase III aducanumab study – in prevention of the disease in pre-symptomatic subjects. But the group frustrated investors by refusing even to comment on whether an interim analysis of its pivotal aducanumab trial would take place, let alone when; Biogen's near-term investment case is riding on this study, due to read out in 2020.

Best possible approach

Speaking to *Vantage* this morning, AC's chief executive, Andrea Pfeifer, said she had been convinced that crenezumab would make it: "We took the best possible approach; we dosed high enough." While stressing that she had not seen the full dataset, she said it looked like prodromal to mild Alzheimer's subjects, which Cread 1 and 2 tested, were already too late in the course of disease.

If this is the case it could arguably favour prevention studies of the sort Biogen plans to start. Crenezumab is

already in such a trial, and Roche is continuing this, along with development of gantenerumab, a Morphosys-derived amyloid-beta MAb (*Preventive Alzheimer's trials keep amyloid hope alive, April 26, 2018*).

"Is prodromal already a phase where tau is too advanced, and contributes too much to the pathology, and we have to use combination therapy?" Ms Pfeifer added. AC has a separate deal with Roche covering the anti-tau MAb RG6100.

Whatever the hopes were for crenezumab to buck the amyloid-beta failure trend, the signs were not good: back in 2014 its phase II Abby and Blaze trials failed. Still, these were in mild to moderate patients, and subgroup analyses hinted at a possible benefit in the mild population.

While yesterday Bernstein opined that if crenezumab showed plaque removal it would be "hard to argue for the lack of read-across to aducanumab", today most analysts played down suggestions that the former's failure might have a read-across to the latter.

True, crenezumab and aducanumab have important design differences, and the Biogen pivotal programme focuses on a slightly milder population, something that could favour the bull thesis. But it cannot be denied that the amyloid-beta hypothesis just took yet another knock, and that cannot be good for Biogen.