Evaluate Vantage

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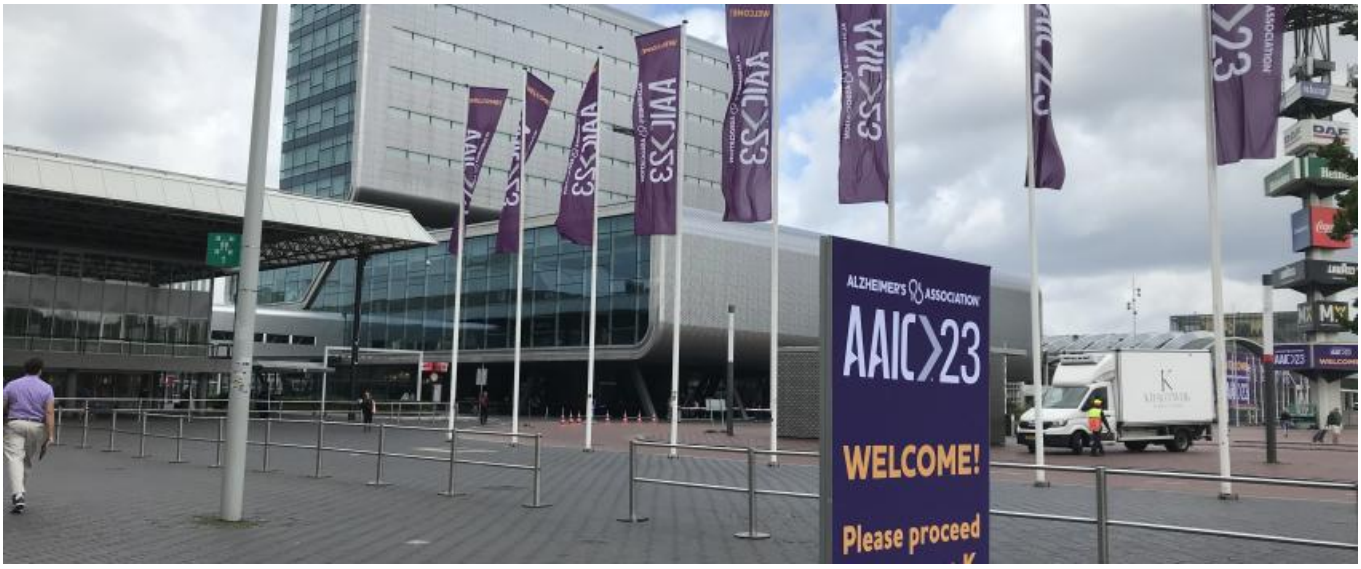
AAIC 2023 – Acumen's new amyloid approach impresses

Madeleine Armstrong



But how different is ACU193 really?

The amyloid-lowering era in Alzheimer's might be only just beginning, but some groups are already trying to improve on existing antibodies. One such company is Acumen, which saw its stock rise 55% yesterday on promising phase 1 data presented at AAIC over the weekend.

Acumen believes that by targeting amyloid-beta oligomers, rather than plaques or protofibrils, it could avoid the Aria-E side effects seen with the likes of Eisai and Biogen's Leqembi and Lilly's donanemab. However, on this point the latest results are far from clear.

The Intercept-AD trial found an Aria-E rate of 10% among 48 patients receiving ACU193, versus none among 14 patients on placebo. This is not all that different from the 13% seen in Leqembi's phase 3 study, Clarity AD, with the caveat that Acumen's trial is small and relatively short.

And with the highest dose of ACU193, 60mg/kg per month, there were three cases of Aria-E, including the only symptomatic case, giving a rate of 21%. For comparison, the recommended dose of Leqembi is 10mg/kg, another factor that makes it difficult to compare the two compounds.

One interesting finding in Intercept-AD was a lack of Aria-E among the six patients who were homozygous for the ApoE4 allele – in trials of other anti-amyloid-beta antibodies, these subjects have been shown to have a greater risk of Aria-E.

Presenting the results on Sunday, Acumen's chief medical officer, Eric Siemers, acknowledged that this could be due to chance in a small study, but said this would be something to watch in future trials.

Aside from Aria, there were three serious adverse events, none of which were deemed related to ACU193. One patient discontinued after a lacunar infarct, which was also ruled unrelated to drug.

Amyloid lowering

Despite the questions over Aria, investors were encouraged by a reduction in amyloid plaque burden in the multiple ascending dose portion of Intercept-AD at 70 days, which Stifel analysts described as an "upside surprise". As ACU193 targets oligomers, Acumen had not been sure that it would see plaque lowering, Siemers said.

He added that the amyloid lowering seen was similar to that observed at three months with Leqembi in Clarity-AD.

When asked whether this amyloid clearance might have been caused by ACU193 hitting plaques as well as oligomers, Siemers told *Evaluate Vantage*: “Maybe you do have a little bit of binding to plaque. None of these things are 100% selective.”

The other possibility, he said, is that binding to oligomers produces an “equilibrium shift” that indirectly lowers plaques – which, he noted, are not static entities. Siemers added that Leqembi targets protofibrils, but still leads to a reduction in plaque.

The study also looked at measures of cognition and cerebral blood flow, but found no benefit with ACU193. This “wasn’t particularly surprising”, though, given the size and length of the trial.

Next up for Acumen, which announced a $100m financing yesterday, will be a phase 2/3 trial, slated to start next year. Siemers said the group plans to evaluate 60mg/kg per month – likely with a titration regimen – and a lower dose which has yet to be decided.

The company also plans to develop a subcutaneous formulation, but this looks a while away. “We have to select the doses for the phase 2/3, but then we also have to see what happens in the phase 2/3 at those doses. And that will determine where we go with the subcutaneous,” he said.

Others focused on oligomers include Cognition Therapeutics and Alzheon, albeit with small molecule approaches. Promis Neurosciences is about to take its oligomer-selective MAb into the clinic, while Prothena’s phase 1 stage antibody PRX012 is said to have activity against all aggregated forms of amyloid including oligomers and plaques.