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Aducanumab: this time it’s personal

Madeleine Armstrong

The focus shifts to whether the FDA will overrule its own panel and approve the Alzheimer’s project.

The US FDA usually, but not always, follows the advice of its advisory committees. And that “not always” seems to be what much of the sellside is clinging to following Friday’s highly negative adcom vote for Biogen’s Alzheimer’s candidate aducanumab.

Many analysts believe that adu could still get the nod at first pass, given the FDA’s strong stance in favour of the project. But after the FDA’s own very positive guidance and the grilling the panel gave adu on Friday, an internal battle could now be brewing, with the agency’s credibility at its core.

That credibility is already looking shaky after the emergency use authorisation, later revoked, for hydroxychloroquine for Covid-19, and the controversial press conference when an EUA was granted for another Covid therapy, convalescent blood plasma.

So, in theory, the FDA should be treading carefully, which would be bad news for Biogen bulls. Indeed, investors today cooled on the chances of adu’s approval, with Biogen’s stock opening down 30%, wiping out the gains it made last week when the briefing documents were released.

“Shockingly positive”

Still, the debate over adu appears to have already got personal, with Billy Dunn, director of the FDA’s office of neuroscience, seemingly determined to get the project approved.

His prepared remarks before the panel were unusually positive – “shockingly positive”, to use the words of Evercore ISI analysts. Mr Dunn even went so far as to describe adu’s one arguably positive phase III study, Emerge, as a “home run”, an assessment that seems highly questionable (*Shock revelation sees Biogen erase its aducanumab losses, October 22, 2019*).

Evercore’s Umer Raffat hinted that there might be another reason for Mr Dunn’s enthusiasm over adu. “There’s feedback going around some investors that he may be looking to leave FDA; he’s very incentivised to be supportive of [adu],” Mr Raffat said during his weekly investor podcast.

Whatever the rationale, there seems to be optimism among some of the sellside that Mr Dunn might have made up his mind to approve adu regardless.

Count the votes!

Even so, it is hard to ignore such an overwhelmingly negative adcom. The most damning vote saw panellists come down 10-0 against on the question of whether the Emerge trial, within the context of the entire adu dataset, could be considered primary evidence of the project's effectiveness. There was one abstention.

Analysts searched for precedents that could support a case for adu's eventual approval despite this rejection. Several noted that historically, the FDA has disregarded the advice of its panels around 20% of the time, apparently referring to a paper published last year. However, most of these cases involved the FDA making more restrictive decisions after favourable committee recommendations rather than the other way around.

The most famous recent example of a negative adcom that did translate into approval concerned Sarepta's Exondys 51, but that vote was closer, at 7-3 against and three abstentions. Stifel found that since 2006 there have been around 20 projects that received zero panel votes in favour of approval. None was approved.

And Salim Syed of Mizuho cited a McKinsey analysis showing that only 3% of projects that received negative adcom votes went on to receive approval. He has largely written off adu's hopes, notwithstanding what he termed a "rogue FDA", giving the project a mere 10% probability of success – a stark contrast to Leerink's 70% even in light of the adcom result.

Steven Seedhouse of Raymond James was more scathing still, writing: "There is no serious scientific argument in favour of anything other than a new prospective study of aducanumab, and we can't explain FDA's effusive stance."

Had the FDA asked Biogen to carry out a new trial the agency might not be in this mess. But in apparently urging the company to file adu on data that could at best be described as incomplete, it has now left itself between a rock and a hard place.