Evaluate Vantage

July 23, 2021

The moral battle lines are drawn in Alzheimer’s

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Biogen goes on the offensive against “misinformation” and a media assault, but Roche says patients want clinical benefit, “not imaging”.

With the FDA’s controversial approval of Aduhelm seen as a lowering of the regulatory bar in Alzheimer’s disease, analysts had expected Roche to pursue a Biogen-like strategy with its beta-amyloid MAb gantenerumab. Yesterday the Swiss group appeared to scotch such expectations, hinting that it wanted to see a clinical benefit and not just biomarker data.

This might have been a sideswipe at its US rival as the companies held simultaneous second-quarter analyst calls dominated by questions about their respective Alzheimer’s projects. Whether Roche would actually follow through on its rhetoric is the big unknown here, but it is clear that this battle has moved beyond polite exchanges of opinion.

Biogen went on its offensive in an open letter to the Alzheimer’s community published alongside quarterly figures. This claimed “extensive misinformation and misunderstanding” over Aduhelm’s approval, which was based on a biomarker instead of clinical benefit, concerned an overhauled analysis of an initially failed trial, and went against an adcom vote.

“Recently … there has been a turn outside the boundaries of legitimate scientific deliberation,” Biogen stated. Last month a Stat exposé said that in 2019 Billy Dunn, director of the FDA’s office of neuroscience, had held an undocumented meeting with Al Sandrock, Biogen’s head of R&D, to discuss Aduhelm, and the claim prompted an investigation to determine whether FDA policies and procedure might have been breached.

Stoking the flames

The first question on Biogen’s quarterly call stoked the flames. Oppenheimer’s Jay Olson asked: “What do you suppose it is about Alzheimer's disease that causes the media to react so negatively to a drug that could actually help patients and their families?”

Biogen’s chief executive, Michel Vounatsos, said he agreed with this premise, adding that the controversy would hit patients the most. He made an interesting comparison with Aids, saying the first HIV antiretrovirals were approved controversially on a biomarker, before viral load reductions, and survival benefit, were later shown.

But his defence of the basis for Aduhelm’s approval was at odds with comments made by Roche about gantenerumab, which some analysts had been expecting the Swiss group to file this year after running a high-

dose, biomarker-focused trial.

The head of Roche's pharma division, Bill Anderson, insisted that his company was "committed to seeing through" gantenerumab's two phase 3 studies, Graduate 1 and Graduate 2, which both test clinical benefit measured by CDR-SB and end in 2022. "We'll be in dialogue with the regulators about every way to accelerate the process of filing," he added.

The obvious question here is what Roche might do if the studies fail to show a cognition benefit but the FDA is nevertheless open to a biomarker-based filing. "What the Alzheimer's community is looking for is a benefit on what matters to patients in their life, and that's not imaging," Mr Anderson stated. "If [gantenerumab] is delivering a clinical benefit then we should see it with our study."

This back and forth, and Biogen's astonishing implication that being sceptical about Aduhelm was an attack on Alzheimer's patients, is of course a sideshow to the business of actually selling the drug. This is largely non-existent at present: second-quarter revenues came in at $1.6m, and analysts estimated that barely 100 patients had been treated commercially since the June 7 approval.

Much of the problem appears to be down to payers hesitating as they await a coverage decision from Medicare in April 2022. Biogen said several scenarios were theoretically possible, including no coverage, coverage with restrictions or coverage for specific patient groups. Until a determination is made hospitals might hesitate to build inventory, some analysts reckon, and Aduhelm sales will be minimal.

For his part, however, Roche's Mr Anderson was clear as to how an Alzheimer's drug secures US reimbursement. "Strong cognitive data is required," he told analysts. "We're not treating imaging, we're treating patients."

Controversy

Again, it must be stressed that only Roche knows how it will proceed with filing, and the group did not expressly rule out relying on biomarkers.

But you can hardly blame Roche for not wanting to get dragged into a controversy that as its bear (and unrealistic) scenario has Aduhelm being pulled from the market. Other companies might also be considering the reputational threat; this year Lilly will file its contender, donanemab, and some expect Eisai to submit its Biogen-partnered lecanemab.

With several now discontinued projects having shown some effect on beta-amyloid the floodgates could open. On the other hand, Mr Sandrock poured cold water on any notion that a host of failed Alzheimer's projects could now be lining up for accelerated approval, saying bapineuzumab's effect, for instance, could have been down to a "spurious" increase in amyloid plaques in the placebo group.

Perhaps the extent of the unknowns analysts are now grappling with was best illustrated towards the end of the Roche call, when Cowen's Stephen Scala asked for confirmation that gantenerumab had not, in fact, already been filed.

"Sure," Mr Anderson replied after a pause. "Yes. It's not already filed."