Evaluate Vantage

January 12, 2022

Aduhelm verdict puts the heat on Biogen – and on the FDA

Jacob Plieth

The US Centers for Medicare & Medicaid Services' national coverage determination for Biogen's Aduhelm makes for uncomfortable reading.

Yesterday's proposal to limit Medicare's obligation to pay for Biogen's Aduhelm could have been worse, but not by much. The draft guidance is so restrictive that, assuming it is implemented, it could result in Aduhelm recording virtually no revenue in the near term.

But it also comes as an apparent slap on the wrists of the FDA: not much reading between the lines is required to see the agency being told that it should never have approved the controversial Alzheimer's disease drug to begin with. The guidance's main thrust is that until Aduhelm shows a meaningful benefit on cognition and function it should not be paid for.

While Aduhelm's accelerated approval is already conditional on a confirmatory study, it seemed unlikely that the FDA would actually pull the drug should such a trial fail years down the line. But the guidance effectively puts pressure on the agency to stick to the conditions of the accelerated approval, as well as making it extremely hard for Biogen to sell any Aduhelm during its conditionally approved phase.

Aduhelm has hardly been prescribed since its approval in June, and Biogen had claimed that doctors were holding off until implementation of the guidance, a national coverage determination (NCD) spelling out the conditions under which all Medicare contractors would have to provide and pay for the drug.

What does it mean?

Few had expected the worst-case scenario of blanket non-coverage, but coverage with evidence development, which the Centers for Medicare & Medicaid Services (CMS) is now proposing, represents a materially worse outcome than the middle ground many analysts had forecast.

In effect it means that Medicare would only cover patients given Aduhelm in randomised, controlled trials that are approved by the CMS, and in those backed by the NIH. Such trials must be conducted in a hospital-based outpatient setting, and meet other criteria.

This was viewed as sufficiently restrictive for Mizuho to remove nearly all Aduhelm sales from its Biogen model yesterday. In a statement Biogen said the draft NCD would almost completely remove Aduhelm coverage for Medicare beneficiaries, and duplicate efforts like Aduhelm's 1,696-patient Embark and 6,000-patient Icare-AD-

US studies.

These two trials are of immediate relevance as more lenient coverage with evidence development might have encompassed them. But, as they have no control arms, if the NCD is enacted per the draft they will not qualify.

Indeed, on the question of available data so far the CMS is scathing, listing 21 phase 3 randomised controlled clinical trials of projects from bapineuzumab to crenezumab alongside those of Aduhelm, and casting doubt on Aduhelm's purportedly positive Emerge trial given its premature halting for futility.

"With conflicting results from Emerge and Engage, and a secondary analysis that did not resolve the difference, CMS believes that the available evidence is insufficient to establish that the treatment is reasonable and necessary," the draft NCD states.

No surrogate biomarker

Further, the CMS appears to slam the FDA's view that brain amyloid-beta plaque reduction is a biomarker capable of backing accelerated approval. The draft instead calls for evidence of meaningful benefit on cognition and function, and says "no biomarker has achieved surrogate status in Alzheimer's".

Randomised Aduhelm data will emerge, eventually: Biogen vows to start screening for Aduhelm's confirmatory trial in May, with primary completion four years after initiation. At least the 1,300 patients expected to be enrolled here might qualify for coverage under the proposed NCD, as long as the study is approved by the CMS.

It must also be stressed that the guidance applies to all amyloid-beta MAbs, and likely raises the bar for what pivotal trials of Eisai/Biogen's lecanemab, Lilly's donanemab and Roche's gantenerumab must show when they yield data this year. Biogen today opened off 10%, but Lilly and Roche fell a more restrained 3% and 2% respectively.

Biogen's next key event is tomorrow's analyst call, at which it will presumably say what it plans to do next. It cannot be underestimated how much Aduhelm now reflects on the tenure of the group's chief executive, Michel Vounatsos.

Clearly, if halving Aduhelm's price was intended somehow to please the CMS it has not worked, though it might yet raise Biogen's standing with patient advocates. Yesterday the Alzheimer's Association called the draft NCD a "shocking discrimination" that proposed to restrict Aduhelm access to "a privileged few – those with access to research institutions".

Such views are relevant because there now follows a 30-day public comment period. The bull case is that pressure groups succeed in persuading the CMS to reverse or water down the draft guidance, with analysts citing the example of Car-T therapies, whose draft NCD was coverage with evidence development (specifically trials and a patient registry), but whose final determination was full coverage.

That said, Aduhelm's draft NCD is so negative that the CMS might already have painted itself into a corner.