Evaluate Vantage

June 07, 2021

Biogen makes history with Alzheimer’s approval

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A green light from the US regulator for aducanumab is a huge boost for Biogen, but not everyone will be celebrating.

Biopharma’s biggest event of the year has swung Biogen’s way. News of aducanumab’s approval sent drug stocks higher; that the FDA is comfortable with ruling against a largely negative advisory committee and has granted approval despite inconclusive clinical data confirms the US agency as one of biopharma’s firmest friends.

The FDA’s nod to the controversial dataset is an accelerated approval, with the requirement to conduct a further study. This is unlikely to appease critics of the decision, however: the trial will take years to conduct and will likely prove tricky to recruit if patients are reluctant to risk getting a placebo.

That means either designing the trial without a control arm – which seems unlikely – or perhaps running it outside the US. Either way, the FDA has previously placed little pressure on developers to get such confirmatory studies under way quickly, meaning that Biogen will have many years of aducanumab revenues to look forward to.

Considering the investment that Biogen has made in Alzheimer’s, this will be a relief to executives and investors, many of whom might have been expecting a huge writeoff in R&D costs. *Evaluate Omnium* estimates that running aducanumab’s clinical trials cost $1.63bn, although total expenditures are likely to be much higher.

A look at the estimated cost of clinical trials across the beta-amyloid MAb projects shows that developers have committed billions of dollars to this mechanism. With today’s news those costs start to look salvageable; Lilly shares jumped a huge 12% in response to the approval of aducanumab, which is now branded Aduhelm.

Targeting amyloid beta: key projects and estimated costs		
Project/indication	**Company/status**	**Estimated total cost of registered clinical trials***
Approved		
Aduhelm (aducanumab)	Biogen/Eisai – approved by FDA June 2021	$1.63bn
Still in development		
Crenezumab	Roche/AC Immune – ph2 in PSEN1 E280A mutation carriers due 2022	$1.01bn
BAN2410 (lecanemab)	Biogen/Eisai – ph3 read out in early disease late 2022	$1.42bn
Gantenerumab	Roche – ph3 readouts in early disease settings due 2022	$2.27bn
Solanezumab	Lilly – ph3 readout in at-risk asymptomatic patients due 2023	$2.80bn
Abandoned		
Bapineuzumab	Pfizer/J&J – abandoned 2013	$2.42bn
**Registered on clinicaltrials.gov. Note: numbers for Lilly's donanemab under review; readouts based on primary completion date in clinicaltrials.gov. Source: Evaluate Omnium.*		

While many believed that the FDA was likely to grant approval, it was assumed that Aduhelm's prescribing information would at least restrict use to certain patients. Instead, the label simply states that Aduhelm is "for the treatment of Alzheimer's disease". This means that it is down to payers to ration the drug, which they will surely seek to do considering the minimal efficacy and toxicity burden – and what is likely to be a high price tag.

In a statement from Dr Patrizia Cavazzoni, the director of the agency's CDER division, the FDA acknowledged that there remains uncertainty about Aduhelm's benefit. But it seems clear that the agency maintained its belief in the drug, an opinion that first emerged in surprisingly positive briefing documents before the advisory committee.

"In all studies in which it was evaluated … Aduhelm consistently and very convincingly reduced the level of amyloid plaques in the brain in a dose and time-dependent fashion. It is expected that the reduction in amyloid plaque will result in a reduction in clinical decline," Dr Cavazzoni said today.

By choosing to grant accelerated approval – which the advisory committee was not asked to consider – the FDA has managed neatly to sidestep the negative panel that followed those briefing documents. But this will not silence those that believe that Biogen should have been required to provide much stronger evidence of this drug's benefits, versus its risks.

Still, the outcome of Aduhelm's regulatory review was always going to be controversial, whatever the FDA decided. While many will be happy to see Alzheimer's patients getting access to what Biogen claims is the first disease-modifying drug, others will feel very uncomfortable about the precedent that this decision sets, in Alzheimer's and beyond.