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BIOCENTURY SPECIAL REPORT: Aducanumab approval



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FINANCE

Right or wrong, the aducanumab decision could turbo-boost investor interest in neurodegeneration

BY C. SIMONE FISHBURN, EDITOR IN CHIEF

If it turns out that the aducanumab approval ushers in an era of accelerated approvals in neurodegenerative disease, FDA's decision may have more impact on the evaluation of risk in the troubled field than on what Biogen's drug does for Alzheimer's patients. The consequence could be a shot in the arm for investment in neurodegenerative diseases across the board.

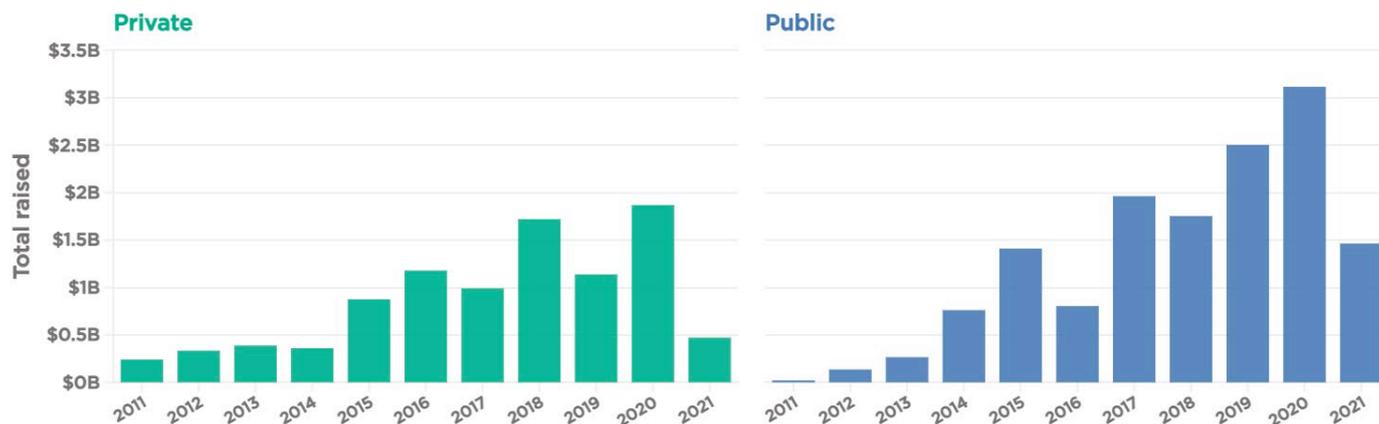
The chances are low that Aduhelm aducanumab from Biogen Inc. (NASDAQ:BIIB) will revolutionize Alzheimer's disease, given the marginal signal in clinical trials — a consensus view among investors and drug developers who spoke with BioCentury. The drug's impact will be partly governed by pricing, access and whether other regulatory authorities follow FDA's lead. Many patients will receive it, but whether this drug alone will put a dent in the global impact of the disease is far from certain.

However, the way, rather than the fact, the drug was approved might alter the risk assessment for investors who for decades have held back, or walked back, their involvement in neurodegenerative diseases due to the long odds. The complaint has been that it's too hard, the trials are too long and the chances of success too low, to warrant grand-scale investment in treatments.

The result has been barely any first-in-class therapies in neurodegenerative disease in or outside of Alzheimer's disease for nearly two decades.

"One of the canonical challenges in R&D in this space are the clinical timelines. So if the takeaway is that these will decrease, that's a huge benefit for the field," Jonathan Behr, partner at SV Health Investors' Dementia Discovery Fund, told BioCentury.

Neurodegeneration company funding, 2011-2021



The DDF focuses on innovations in the dementia field outside of the amyloid hypothesis. Biogen is a limited partner in the fund.

While the circumstances around Aduhelm’s approval remain highly controversial, drug developers in neurodegenerative diseases have long been hoping to see accelerated approval pathways and use of surrogate endpoints. FDA’s new-found openness to that — articulated by Center for Drug Evaluation and Research director Patrizia Cavazzoni at a press briefing Monday — is being welcomed by many in the field.

“That’s true for small and large companies. And it’s independent of whether or not you feel strongly about amyloid as an endpoint,” said Behr.

The difference isn’t only in shortened timelines and lower costs, which investors hope is the consequence of the new policy, but also in the probability of success.

“One of the biggest impediments to working in neuro has been really mushy endpoints,” Venrock partner Camille Samuels told BioCentury. The probability of technical success either is — or is perceived to be — about 2% in neuro, she said. “We’re constantly thinking about, even though this is preclinical, what are the clinical endpoints going to be? Are they precedented? To what extent can we use surrogates? You think about that all the time,” said Samuels.

With money at record levels in the biotech ecosystem, a better risk profile in neurodegeneration might also offer a new destination for investors looking to diversify outside of oncology.

“I would expect excess capital to go into various flavors of neuro,” said Samuels.

The implications could also be a boon for small companies, which don’t have the resources to attack Alzheimer’s in the old paradigm, according to Behr. “If there is a paradigm shift, which the door is open to, this becomes a much more possible set of indications for smaller companies.”

Catalytic benefits

Surrogate endpoints could be a game-changer in neurodegeneration because they can move the inflection point for value creation earlier in the development pathway. Accelerated approvals bring separate and related benefits.

Diseases that require cognitive endpoints to show clinical efficacy involve subjective assessments, often via questionnaires, to create complex numeric scores such as CDR-SB (clinical dementia rating scale sum of boxes) in AD. Investors view those endpoints as high risk because of their low accuracy, a problem that is mitigated if biochemical, quantifiable markers can be used as surrogates.

Moreover, those endpoints can’t be used across all phases of development because the statistics don’t bear up with smaller patient numbers.

“Phase II didn’t read onto Phase III — you didn’t have the time and number of patients in your Phase II to be able to look at the same endpoint in Phase III,” said Samuels.

That means the catalyst could come sooner.

“Public investors hate changing endpoints between Phase II and Phase III. And so if surrogate markers are both your Phase II endpoint and then an approvable endpoint, that’s game-changing in terms of how much value accrues to the company with Phase II data, as opposed to having to wait for Phase III data.”

That pattern has also borne out in oncology, where investors await readouts of efficacy that can come in Phase II and even sometimes Phase 1b trials.

Both time and costs can go down for the trials as well. The greater precision of surrogate endpoints compared with survey-based endpoints means it’s easier to get statistically significant answers from smaller groups of patients, said Behr. And trials can also get shorter because surrogate endpoints often show changes long before the clinical effect.

If the accelerated approval process now becomes available to more neurodegeneration therapies beyond amyloid reduction agents, it could have a transformative effect on investment in the space, say the investors. “It drastically lowers the cost in the most costly portion of development,” said Behr.

On top of the time factor, said Samuels, is the issue of who pays for the costly trials.

“Approval is the pot of gold at the end of the rainbow,” said Samuels. Normally, the cost burden is all on the company and investors to reach that point. But with accelerated approval based on surrogate endpoints, the extensive post-approval confirmatory trials can be funded at least in part by revenues.

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JONATHAN BEHR, SV HEALTH INVESTORS

“At least you’re then doing it with that old-fashioned thing called retained earnings, paying for it from profits rather than with pure equity dollars,” said Samuels. “Funding the trials with the profits from your revenue is so much less costly than if it’s done with my dollars or even public dollars.”

Behr said he’s wary of over-generalizing about what happened with Aduhelm to other diseases, and though FDA’s actions raised more questions than answers, the decision still marks a new page. “All these doors are open to discussion that weren’t being asked before.”

A leaf from the cancer playbook

The hope is that neurodegeneration can benefit from accelerated approvals and surrogate endpoints in the way cancer has. At the same time, Aduhelm’s approval has also brought some of the thorny issues to light that are clouding the pathway’s use in cancer.

Biology advances in neuroscience have started to change perception of risk in the field, with investment, as well as deal flow, picking up for both public and private companies.

Still, the investment totals are dwarfed by cancer, which garnered about nine times the amount raised by neurodegeneration companies in venture funding over the last decade, according to data from BioCentury’s BCIQ database.

At Monday’s press briefing, Cavazzoni tied progress in cancer to implementation of accelerated approvals.

“The accelerated approval pathway has been an incredibly useful tool in oncology,” Cavazzoni told reporters. “For those of you who have followed the dramatic leap forward in the cancer space in the last 20 years, we believe it serves as a model that we hope can be replicated with neurodegenerative diseases.”

Two-thirds of accelerated approvals granted from 1992 to the end of 2020 were in cancer, with another 13% in HIV — the original impetus for allowing approvals based on surrogate endpoints. None were in neurodegeneration.

Behr said the long timelines and the costs in Alzheimer’s disease have previously chilled sentiment in the public markets.

“From an investor perspective the costs and timelines are important dependently and independently,” said Behr. For example, an Alzheimer’s Phase II or III trial may require tenfold or more patients than a cancer or rare disease trial, and patients will be on drug for one to two years, as opposed to months. “So with pivotal Alzheimer’s trials costing around \$100 million or much more, the generalist investor’s path to the stage of development that public markets value is much longer. So why choose that?”

The argument in neurology has been that the unmet need and market are so huge that they compensate for the time and investment. The risks and likelihood of success have changed over time, said Behr. “As we gain more insight and understanding, we’re decreasing the risk.”

The Aduhelm approval, however, stoked a controversy and struck at the heart of one of the issues surrounding surrogate endpoints in cancer because of the lack of direct evidence tying the reduction in β -amyloid plaques with improvement in cognition.

“Treatment with Aduhelm was clearly shown in all trials to substantially reduce amyloid beta plaques. This reduction in plaques is reasonably likely to result in clinical benefit,” wrote FDA in its statement announcing the drug’s approval.

Speaking on a video interview hosted by Prevision Policy Wednesday, Richard Pazdur, director of FDA's Oncology Center of Excellence, called the "reasonably likely" language in the current legislation one of his "big bugaboos."

Noting that cancer has benefitted from accelerated approval, Pazdur said the field has been transformed by the pathway over the last few decades. Most of the drugs under accelerated approval demonstrated their full benefit after having been approved on single-arm studies.

"We've been blessed with the endpoint of response rate" said Pazdur, and though it may be a long stretch, an analogy could be drawn between response rate and the reduction in amyloid. Response rate seen in tumor shrinkage takes place after drug treatment, much as clearance of amyloid is the result of drug treatment. "That's prima facie evidence that there is a biological effect of the drug and hence one can use it for this boogeyman of substantial evidence that one requires."

Pazdur emphasized that the decision of whether amyloid reduction translates into something clinically meaningful is not his domain, and he did not doubt the applicability of accelerated approval.

But the "surrogate, reasonably likely to predict clinical benefit" provision in the current legislation is problematic, he added.

"First of all, you're either a surrogate or you're not a surrogate," said Pazdur.

"If one takes a look at the Prentice criteria for surrogacy, it is quite stringent," said Pazdur. "Response rate, time to progression, disease-free survival. None of these are surrogates, and we have to be scientifically honest with this."

"I THINK WE HAVE TO CLEAN THIS UP. I'D LIKE TO EMPHASIZE THAT A CORRELATE DOES NOT MAKE A SURROGATE."

RICHARD PAZDUR, FDA

He added: "They're evidence perhaps of early clinical endpoints. They're at least evidence of biological activity. But they are not surrogates. So I think we have to clean this up. I'd like to emphasize that a correlate does not make a surrogate." PD-1 has provided numerous examples in cancer of survival improvements without PFS or response rates and vice-versa, he noted.

It's not clear whether the amyloid controversy will add fuel to this conversation, but new avenues for biomarkers in neurodegeneration, even if they require a revamping of stringency, are broadly seen by the field as a positive. Some believe that FDA will be more open to use of biomarkers for slowly progressing diseases for which it is hard to prove clinically meaningful outcomes than for rapidly progressing diseases such as amyotrophic lateral sclerosis (ALS).

And regardless of whether Aduhelm or another amyloid-lowering agent becomes widely used, opportunities have opened up for more companies. "The pipeline is meant to be additive," said Behr, reflecting broadly held views that combination therapies will be needed to solve Alzheimer's disease, a fact now commonplace in cancer.

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