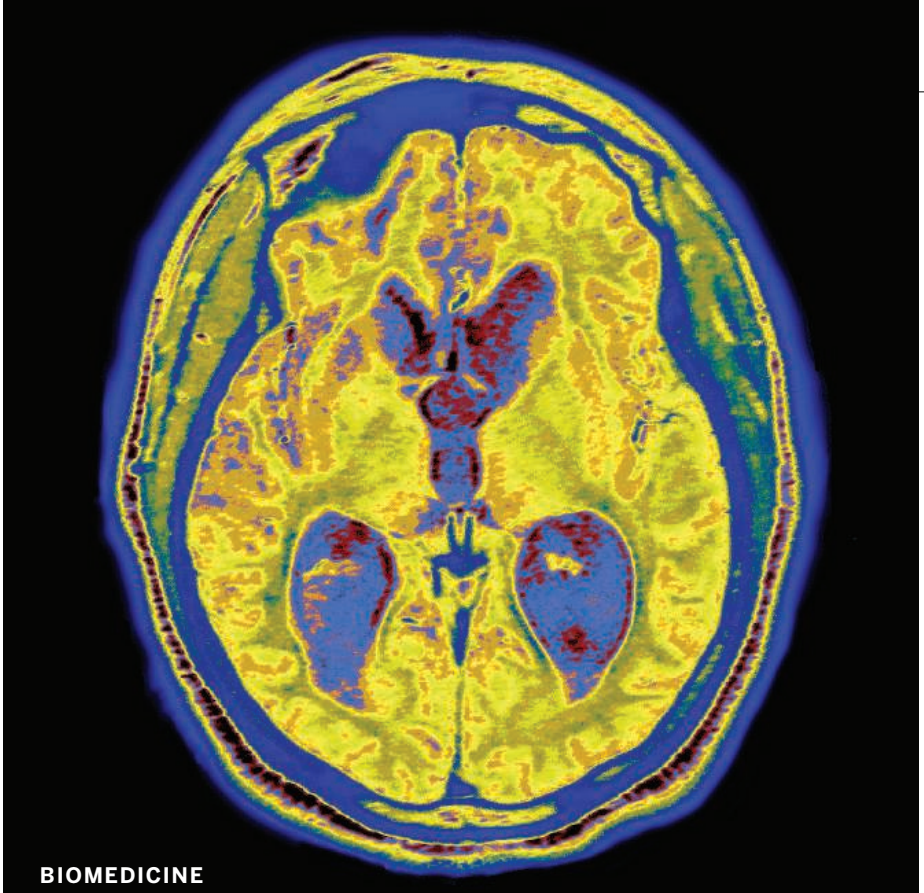

A new antibody drug aims to slow the cognitive decline of Alzheimer's disease, a fatal disorder that has caused this patient's brain to atrophy.

IMAGE: JAMES CAVALLINI/SCIENCE SOURCE

BIOMEDICINE

Alzheimer's drug approval gets a mixed reception

FDA allows use of antibody despite ongoing debates over its benefits and dangers

By **Jennifer Couzin-Frankel**

Last week's Food and Drug Administration (FDA) approval of the first Alzheimer's drug to clearly slow the disease's cognitive decline prompted cheers in many quarters, but consternation in others. The benefits of the drug, an antibody called lecanemab, appear modest and have only been shown in people with early Alzheimer's. It also comes with serious side effects including brain swelling and bleeding.

Still, the prospect of finally having something to offer people with a ruinous neurodegenerative disease has won over many scientists and physicians. "I'm on the side that it's not perfect, but it's a step in the right direction," says Joy Snider, a neurologist at Washington University School of Medicine in St. Louis who was part of the recent phase 3 trial that demonstrated the drug's efficacy—but also highlighted its potentially grave risks.

Now, a second U.S. regulatory agency must decide whether to reverse a controversial stance that would preclude federal reimbursement for the drug outside of clinical trials. The treatment, which must be given intravenously every other week, requires close monitoring and is likely to cost tens of thousands of dollars a year.

Hospitals and medical groups are now weighing guidance on which people should be offered the antibody. Sam Gandy, a neurologist at the Icahn School of Medicine at Mount Sinai, is on a committee there that's developing guidance for its hospital. He believes that "it's a fairly small minority of patients" that will qualify, about 20% of those with early Alzheimer's. One reason is that Gandy prefers not to go beyond the profile of participants in the phase 3 trial, which excluded people with various preexisting conditions such as a history of stroke.

Another is the side effects that emerged during the nearly 1800-person clinical trial. The antibody is designed to clear or prevent the creation of amyloid plaques, protein deposits in the brain that are thought to propel cognitive decline and other symptoms of Alzheimer's disease. But such drugs can put patients at risk for the mix of brain bleeds and swelling known as ARIA, which stands for amyloid-related imaging abnormalities, perhaps because the antibodies also strip amyloid deposits in blood vessel walls, weakening them.

In the phase 3 lecanemab trial, the danger of ARIA appeared greater for patients also taking drugs that prevent or dissolve blood clots. Two people given those drugs while taking lecanemab as part of an extension of the trial died after brain bleeds or swelling, *Science* and *STAT* have reported, and some others had serious brain injuries.

Data from the phase 3 trial haven't yet been submitted to FDA, which made its decision based on earlier, smaller trials. But the agency was also familiar with basic findings of the large trial, which were published in November 2022. In a 54-page summary report describing its reviewers' analyses, FDA said it can't pin any of the trial deaths on lecanemab. The drug's main developer, the Japanese biotech Eisai, and its U.S. partner Biogen have taken the same position.

Yet in approving the drug, FDA recommended "additional caution" in prescribing it to people taking blood thinners. And *Science* learned that in July, Eisai distributed a revised consent form alerting trial participants that the risk of a major brain bleed in people on both the antibody and blood thinners "is estimated to be more than 1 in 100 people, but less than 5 in 100 people." The form noted that bleeding "can be serious and can even lead to death." Gandy says he would advise "virtually all" patients on anticoagulants "not to proceed" with lecanemab treatment.

People with two copies of *APOE4*, a gene variant that increases risk for Alzheimer's, also seem at higher risk of ARIA. For example, 9.2% of people with two copies of the variant had symptomatic brain swelling in the pivotal lecanemab trial, compared with 1.4% with no copies. And a third death in the lecanemab trial, which *Science* recently described, involved a 79-year-old woman who had two copies of *APOE4*. She died in mid-September, days after experiencing what looked like a stroke at a restaurant; doctors who treated her at a hospital found extensive brain swelling and bleeding.

Several neurologists who reviewed the woman's case for *Science* said lecanemab was likely the culprit in her death. FDA noted that it has requested MRI images and the autopsy report on the woman, but "the applicant has not been able to obtain additional

information as of January 3. … The available information does not change the risk-benefit assessment for this review."

People with Alzheimer's disease aren't routinely tested for *APOE4* because it hasn't so far guided diagnosis and treatment. Although some scientists had hoped FDA would rule against giving lecanemab to people with two copies of *APOE4*, the agency instead suggested people "consider testing" for *APOE4* status "to inform the risk of developing ARIA when deciding to initiate treatment." Gandy's hospital expects to offer testing for *APOE4* to those interested in lecanemab, to help them better gauge their risk from the therapy.

The drug label approved by FDA also recommends that anyone taking lecanemab have three MRIs over roughly the first 6 months of treatment to watch for side effects, as well as an MRI before beginning treatment. Some scientists had hoped the agency would require that lecanemab be enrolled in FDA's Risk Evaluation and Mitigation Strategies (REMS) program for medications with "serious safety concerns." REMS can require that physicians prescribing a new drug report side effects to FDA, that the drug be administered in qualified health care settings, and that doctors get training about which patients may be at highest risk of dangerous side effects.

FDA did note that it's requesting "expedited reporting" of any deaths in ongoing trials and deaths from significant brain hemorrhages in people who take lecanemab postapproval. University of Cincinnati neurologist Alberto Espay also worries about recipients of the antibody who may develop less severe ARIA. For at least some of them, he says, "I cannot imagine it's irrelevant or inconsequential."

Discussion of these safety concerns comes amid continued debate over lecanemab's benefits. On an 18-point cognition scale, those getting the drug on average declined 0.45 points less than those getting placebo after 18 months. Neurologists disagree over whether patients and caregivers would perceive this difference. "It's really on the edge" of what's meaningful, says Lon Schneider, a geriatric psychiatrist at the University of Southern California Keck School of Medicine. The drug is "approvable, but like many medications that are approved it leaves much to be desired."

Others, such as Snider, say the benefits may well be noticeable. On the part of the scale that assesses orientation, she notes, an individual who scores 0.5 "can still drive" and get around independently. "If you go to a one, you're going to start getting lost."

The Alzheimer's Association, which has come out in favor of lecanemab, celebrated FDA's thumbs-up. And in the lead-up to the agency's decision, more than 200 researchers and physicians signed an open letter that endorsed the drug. Nearly half are recent consultants or grant recipients of Eisai or Biogen, *Science* has found.

Espay, however, argues FDA had painted itself into a corner with an earlier decision. He says officials "are victims of an artificially low bar" they set in 2021 when they approved another anti-amyloid antibody, aducanumab, even though FDA's advisory committee had voted against approval and the evidence that the drug worked was weak. (Last month, a congressional report described that approval process as "rife with irregularities.")

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> **Lon Schneider**, University of Southern California Keck School of Medicine

Both drugs were approved under FDA's accelerated approval pathway, which allows for decisions based on "surrogate endpoints," biological measures thought to predict clinical benefits to patients. In May 2022, Eisai had asked FDA to approve lecanemab based on evidence that it is highly effective at clearing the brain of amyloid plaques, the same surrogate endpoint cited in the aducanumab approval.

Many of the same FDA officials reviewed both drugs, and in both cases, the lead biostatistician, Tristan Massie, expressed hesitations. In the summary report for lecanemab, Massie questioned whether the surrogate endpoint "is reasonably likely to predict change on the clinical outcome." His colleagues didn't agree. "The Division notes the issues that Dr. Massie has raised but, overall, the findings" on amyloid plaques "appear robust and persuasive," they wrote.

But it's unclear whether the Centers for Medicare & Medicaid Services (CMS), the federal agency that pays for many treatments for older Americans, will reimburse for lecanemab. In April 2022, CMS announced it would decline to reimburse for aducanumab, except in certain clinical trials, tanking its commercial prospects. CMS also said it would only consider covering such anti-amyloid antibodies after full FDA approval.

In a statement after FDA approved lecanemab, the Alzheimer's Association called that stance "harmful and unfair" and called on CMS to reverse its position. ■

With reporting by Charles Piller, whose work was supported by the *Science* Fund for Investigative Journalism.

ANIMAL RESEARCH

FDA no longer has to require animal testing for new drugs

Agency can rely on animal-free alternatives before human trials

By **Meredith Wadman**

New medicines need not be tested in animals to receive U.S. Food and Drug Administration (FDA) approval, according to legislation signed by President Joe Biden in late December 2022. The change—long sought by animal welfare organizations—could signal a major shift away from animal use after more than 80 years of drug safety regulation.

"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

In place of the 1938 stipulation that potential drugs be tested for safety and efficacy in animals, the law allows FDA to promote a drug or biologic—a larger molecule such as an antibody—to human trials after either animal or nonanimal tests. Drake's group and the nonprofit Animal Wellness Action, among others that pushed for changes, argue that in clearing drugs for human trials the agency should rely more heavily on computer modeling, "organ chips," and other nonanimal methods that have been developed over the past 10 to 15 years.

But pro-research groups are downplaying the law, saying it signals a slow turning of the tide—not a tsunami that will remake the drug approval process overnight. Jim Newman, communications director at Americans for Medical Progress, which advocates for animal research, argues nonanimal technologies are still "in their infancy" and won't be able to replace animal models for "many, many years." FDA still retains tremendous discretion to require animal tests, he notes, and he doesn't expect the agency to change tack anytime soon.