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# Alzheimer's drug sparks hot debate over benefits as risks like brain bleeding emerge

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Eisai Co. unveiled much-anticipated findings on its experimental Alzheimer's drug, providing tinder for the hot debate over whether its modest efficacy is worth potential risks that include serious brain

bleeding.

Lecanemab, developed with help from collaborator Biogen Inc., pulled large amounts of an Alzheimer's-linked protein from the brain while slowing decline in mental capabilities and daily activities by 27% over 18 months, according to a commonly used rating scale. Yet this came at the price of side effects including brain swelling and bleeding that occurred in about 22% of people on the drug, compared to 10% of those who received a placebo.

The results are the main event at the often-sleepy Clinical Trials on Alzheimer's Disease conference in San Francisco, and mark the first time a drug aimed at slowing the brain disease has generated unambiguously positive results in a final-stage trial.

Eisai's shares, after swinging at the open of Tokyo trading Wednesday, were up about 2.5% at 10:39 a.m. local time, while Biogen was halted.

Still, the benefits of the drug appear modest, said Lon Schneider, a professor of psychiatry and neuroscience at the University of Southern California Keck School of Medicine.

"This is a very small effect, and the debate is going to be about whether it is clinically meaningful," Schneider said in an email. However, the findings provide an opportunity "to assess subgroups that might have preferentially improved."

Five presentations from researchers at Japan-based Eisai, Yale University and elsewhere were to delve into the benefits and side effects in great detail Tuesday. While most cases of swelling and bleeding weren't symptomatic, they sometimes led to headaches, visual disturbances, confusion or worse. There were five large brain hemorrhages in patients who got the drug, compared to just one in the

placebo group, according to results from the trial published in the *New England Journal of Medicine*.

The journal report doesn't include two widely publicized patient deaths that occurred in the extension portion of the trial, when all subjects, including those on placebo, were offered the drug. Both deceased patients were taking blood thinners that may have contributed to bleeding in the brain.

"Both cases had significant comorbidities and risk factors including anticoagulation contributing to macrohemorrhage or death," the company said. "Therefore, it is Eisai's assessment that the deaths cannot be attributed to lecanemab."

In an interview before the meeting, Michael Irizarry, Eisai senior vice president of clinical research, said there were "complicating factors" in both cases. In one, a man in his late 80s who had multiple other medical conditions suffered a heart attack following a brain hemorrhage. An examination indicated that the cause was cardiopulmonary, meaning the doctor's opinion was that hemorrhage likely wasn't the main cause of death, Irizarry said.

In the other case, a 65-year-old woman was given the blood thinner tPA after a stroke, leading to a fatal brain bleed. Such hemorrhages are known side effects of tPA, Irizarry said. In the main, placebo-controlled portion of the trial, no difference in death rates was found between those on the drug and those on a dummy treatment. One patient who received only a placebo and had a hemorrhage also died, the company said.

One unanswered question hovering over the San Francisco meeting is why the Eisai trial succeeded when similar drugs produced ambiguous or negative results. Both lecanemab and Roche Holding AG's gantenerumab target amyloid, an abnormal protein in the brain linked to Alzheimer's

disease, as a way to slow patients' mental decline. Roche is slated to report detailed findings from two large, failed studies Wednesday at the conference.

The key issue is whether the modest slowing of the disease is meaningful to individual patients and their families, especially in light of the potential side effects. While both groups continued to decline during the study, lecanemab was associated with a roughly half-point less decline on an 18-point rating scale that combines measures of cognition, memory and ability to perform daily activities.

While the trial lasted only 18 months, the disease itself can play out over a decade or more, and researchers don't know whether the drug's benefits would grow over time.

The results show "lecanemab will provide patients more time to participate in daily life and live independently," according to the Alzheimer's Association, which called for approval of the medication. "It could mean many months more of recognizing their spouse, children and grandchildren. Treatments that deliver tangible benefits to those living with mild cognitive impairment due to Alzheimer's and early Alzheimer's dementia are as valuable as treatments that extend the lives of those with other terminal diseases."

The details will be pored over both by regulators at the Food and Drug Administration as well as U.S. Centers for Medicare and Medicaid Services officials, who would decide whether and for whom to cover the drug. Medicare, the U.S. health program for older people, all but rejected an earlier Biogen Alzheimer's drug called Aduhelm, only covering it for research purposes rather than as a standard treatment.

That drug's accelerated U.S. approval in 2021 was controversial because of conflicting efficacy results from two large trials. Biogen ended most

of its marketing efforts after Medicare's payment restrictions.

Eisai has applied for accelerated U.S. approval based on lecanemab's ability to lower amyloid, and the FDA is expected to make a decision by early January. If it is approved, Eisai plans to rapidly submit the efficacy data from the trial in order to get full approval. The hope is that a rapid airing of the data, warts and all, will convince Medicare to broadly cover lecanemab.

Even so, requirements such as scanning patients' brains to determine their pre-treatment amyloid levels may stand in the way of widespread use for at least a few years, according to Takeshi Iwatsubo, a neuropathologist at the University of Tokyo's Graduate School of Medicine who will lead a session at the conference Wednesday.

"It's a unique, complex drug that must be used by specialists," Iwatsubo said in an interview. "But the number of dementia specialists and PET-scan facilities are limited, and the capacity is a huge issue."