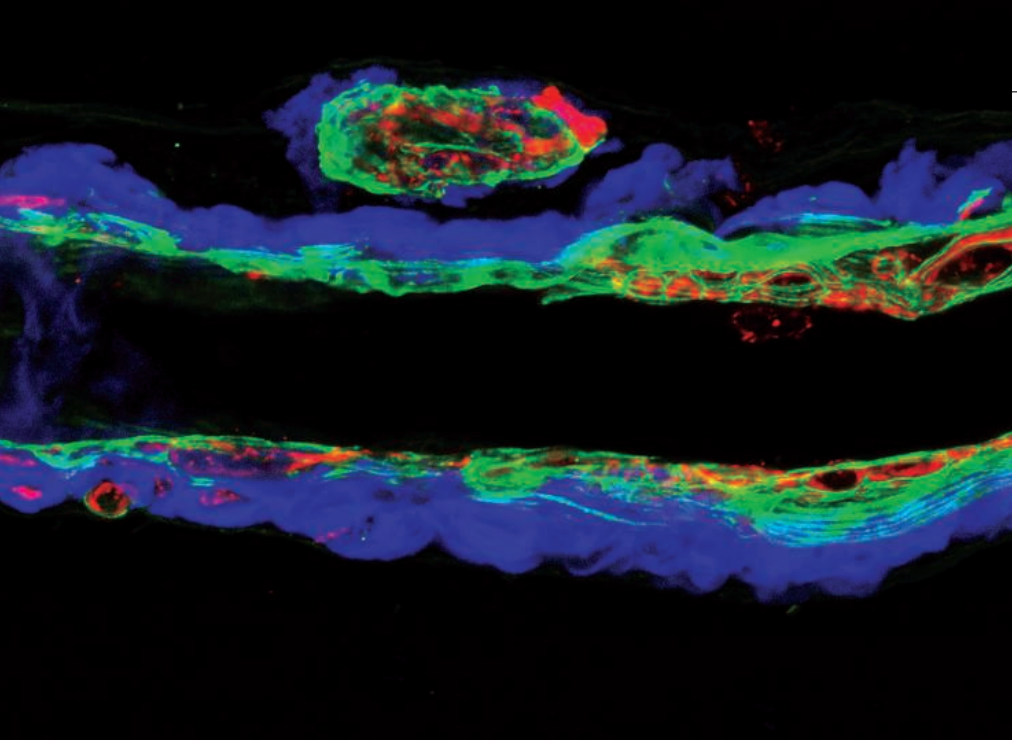

Brain blood vessel membranes (green) can be we
and prone to bleeding after antiamyloid treatments.

BIOMEDICINE

New Alzheimer's drug clears FDA advisory vote despite unknowns

Pivotal trial of Eli Lilly's donanemab leaves questions about how to prescribe it and minimize risks

By **Jennifer Couzin-Frankel**

Nearly 18 months after a novel Alzheimer's drug hit the U.S. market, a sister therapy is poised to get a green light. Advisers to the U.S. Food and Drug Administration (FDA) voted unanimously this week in favor of the monoclonal antibody donanemab, a drug that mops up the toxic protein beta amyloid in the brains of people with early Alzheimer's disease, and modestly slows their cognitive decline.

Now, the agency must decide whether to approve the treatment, and it will have to wrestle with knotty questions. Not only does donanemab, like its predecessor, carry serious risks of brain swelling and bleeding, but the drug's sponsor, Eli Lilly & Co., made trial design choices that create uncertainties about how best to use it in the real world.

The already-approved antiamyloid therapy lecanemab, which is marketed by Biogen and Eisai as Leqembi, slowed cognitive decline in early Alzheimer's patients by 27%. Donanemab did slightly better in its 1736-person phase 3 trial, but the trial had a wrinkle. Participants had to have buildup in their brains of the protein tau, considered a marker of disease stage, which can be detected in positron emission tomography (PET) scans. Although donanemab doesn't target tau, Lilly theorized it might be tough to see benefit in people who didn't have measurable tau in their brains because their disease is likely progressing very slowly.

The company also suspected that those with low or middling levels of tau would be a sweet spot for the drug—far enough into disease to be experiencing cognitive decline that could be monitored in an 18-month trial, but early enough that the treatment would have a better shot of helping them. That theory held: People with low or medium tau had a 36% slower rate of cognitive decline compared with placebo. When the high tau group was included, that improvement dropped to 29%. There remain questions about whether patients and caregivers would be able to detect these differences.

Identifying the patients most likely to benefit from therapy based on their tau levels would be "very attractive" to clinicians, says Jason Karlawish, co-director of the Penn Memory Center at the University of Pennsylvania, who wasn't involved in the studies. "The problem is that getting a tau scan is costly," running thousands of dollars. Several committee members also noted that tau PET scans are complex to interpret and only available at specialized centers.

At the meeting, FDA and company officials argued such scans would not be needed to prescribe donanemab. Kevin Krudys, FDA's clinical efficacy reviewer for the drug, suggested that as with lecanemab, patients would need to have evidence of brain amyloid and early Alzheimer's symptoms to qualify for treatment. Still, expecting a treatment response in people who are largely tau-free requires something of "a leap of faith," because no such patients were included in the phase 3 trial, said advisory committee member Merit Cudkowicz, a neurologist at Massachusetts General Hospital.

Another feature of Lilly's trial design was that monthly infusions of donanemab were stopped once participants' brain scans showed minimal to no amyloid. (Lecanemab, in contrast, is recommended to be taken indefinitely.) Lilly officials said they couldn't justify continuing the therapy when its target had largely vanished, which they noted happened in two-thirds of participants after 1 year, and in three-quarters at 76 weeks, when the study concluded. The company didn't detect an acceleration in cognitive decline after halting treatment, and saw just a minimal uptick in detectable amyloid in some patients.

Physicians at the meeting praised the strategy as a way to avoid exposing patients to unnecessary treatment—but noted participants weren't followed off-treatment for long. "We need longer term studies," said Reisa Sperling, a neurologist at Brigham and Women's Hospital who spoke on behalf of Lilly at the meeting. Furthermore, Krudys noted, "There's considerable uncertainty regarding the appropriate threshold" for halting infusions. And once amyloid levels creep up, the question of when to restart treatment "is still untested," he added.

"Those are questions I would eventually want to have an answer to practically implement this," said Kathleen Poston, a neurologist at Stanford University and committee member.

Looming over donanemab and the rest of this drug class is the risk of brain swelling and bleeding, together known as amyloid-related imaging abnormalities (ARIA). In its pivotal trial, Lilly reported ARIA in 37% of the 853 participants getting donanemab, compared with 15% in the placebo group. Most cases were asymptomatic, but some were serious, and three people on donanemab died from these complications.

PHOTO: WILBER ROMERO FERNANDEZ

Two more died during a subsequent open-label safety study, in which everyone could opt for donanemab. Deaths from ARIA were reported in the lecanemab trials as well.

A particular worry is that the risk of ARIA might translate to tragedy if patients receive a common clot-busting treatment for stroke. The symptoms of ARIA and stroke can overlap—yet certain drugs that are standard therapy for stroke may exacerbate the brain effects of ARIA or potentially trigger brain bleeding in patients on the antibodies. One 72-year-old on donanemab developed symptoms that may have been misdiagnosed as stroke, was given standard clot-busting treatment, and then had a fatal brain hemorrhage. In a lecanemab trial, a patient on the drug also died after getting a clot-busting stroke drug.

Because older people are already at higher risk of stroke, doctors are "between a rock and a hard place" when they treat people on antibodies who have stroke symptoms, acknowledged Teresa Buracchio, director of the Office of Neuroscience at FDA's Center for Drug Evaluation and Research. She noted that FDA would encourage educating physicians on these risks and how to identify ARIA, among other measures.

Physicians are already riding this learning curve as prescriptions of lecanemab pick up. At the Barrow Neurological Institute, neurologist Marwan Sabbagh has prescribed it to about 30 of his patients. (Sabbagh, who spoke in the public session of FDA's meeting urging approval of donanemab, has been a paid adviser to the makers of lecanemab.) So far, he's seen few serious side effects in his patients. He's identified five cases of ARIA, four of which were asymptomatic and resolved.

The fifth patient, who had a more severe case, had sought lecanemab despite carrying two copies of the *APOE4* gene variant, which raises the risk of both Alzheimer's and ARIA. "I've been scared to death" of giving the drug to people in this group, Sabbagh says. Like other practitioners, Sabbagh is testing patients for *APOE4* when considering whether they're good candidates for antiamyloid therapy. Researchers are divided over whether to treat patients who have been informed of the hazards, which FDA also noted in the label for lecanemab.

As their time on lecanemab continues and amyloid levels recede, some of Sabbagh's patients have asked whether they might stop the drug—as the donanemab trial participants did. He doesn't feel comfortable doing that yet, but in some cases is considering spreading out doses. Sabbagh acknowledges that safety "hangs over both these drugs." But he's hopeful that careful clinical decisions can dial down the risk. ■

PHILANTHROPY

Winners of prestigious Sackler prize call for name change

Biophysics prize from Tel Aviv University bears the family's name despite its role in opioid epidemic

By **Jop de Vrieze**

In early May, three biophysicists—Petra Schwille, Cees Dekker, and Leonid Mirny—received emails from Tel Aviv University with some exciting news: They had won the school's Raymond and Beverly Sackler International Prize in Biophysics, the most prestigious award in their field. Each would also receive a share of a $50,000 prize pot.

The scientists were elated, but later realized the prize was sponsored by a family that is notorious for its central role in the opioid crisis that has claimed hundreds of thousands of lives in the United States alone. "It might be naïve, but I did not know about the Sacklers' role until some journalists pointed me [to] it," says Dekker, from the Delft University of Technology. Now, in the latest round in a fight over whether science prizes and research facilities should bear the name of a family that made drugs linked to addiction and fatal overdoses, the three new laureates say they support renaming the prize. "It is never too late to counteract the name washing that the Sackler family did through their philanthropy," says Mirny, from the Massachusetts Institute of Technology.

> **"It is never too late to counteract the name washing that the Sackler family did through their philanthropy."**
>
> **Leonid Mirny**, Massachusetts Institute of Technology

He proposes naming the prize after two of its early recipients who died a few years ago and whose contributions to the field of biophysics are unparalleled: Howard Berg and George Oster. "The name Sackler has really nothing to do topically with biophysics," adds Schwille, from the Max Planck Institute of Biochemistry. "And if it is their philanthropic wish to benefit science, it would also work without the explicit naming."

Tel Aviv University declined to comment on the link between the prize and the family, or on renaming the award and similarly named ones for chemistry and physics. This isn't the first time that the school has come under pressure about its close ties to the Sackler family. After initial resistance, it renamed its medical school for U.S. and Canadian students in 2022 and its Faculty of Medicine in 2023.

The Sacklers and their company, Purdue Pharma, aggressively marketed opioids such as OxyContin, reframing the painkillers as not just for terminal cancer patients, but for a range of milder and chronic complaints. The company downplayed the addictiveness and dangers of these drugs and allegedly directed doctors to overprescribe them. The subject of several lawsuits, Purdue Pharma has admitted criminal wrongdoing, and the U.S. Supreme Court is considering a bankruptcy deal that would require it to pay $6 billion to address opioid addiction and compensate victims and their relatives.

The Sackler family donated substantial sums to art and scientific institutions, in exchange for those organizations displaying its name. The family also arranged lectures on pain medication to medical professionals at institutions it funded, says Massachusetts-based artist and activist Domenic Esposito. Tufts University, the University of Oxford, and Leiden University are among those who have removed the Sackler name from libraries and programs.

Schwille earned her share of the Sackler biophysics prize for creating synthetic cells made up of simplified components, testbeds for determining the minimal prerequisites for life. Mirny predicted that DNA inside cells is folded up and organized by specialized proteins forming molecular motors, a process called "loop extrusion." Dekker provided the first demonstration of this loop extrusion, and developed new ways to use nanopores to sequence DNA and proteins.

Although the laureates object to the prize's name, they say not accepting it would be a step too far. "I think declining a prize is like demolishing a building that carries a certain name," Mirny says. "It's much wiser to rename the building." ■

Jop de Vrieze is a science journalist in Amsterdam.