After Failed Trials, Drug Company Pivots to Early-Stage Alzheimer's

A little over a year ago, Dr. Husseini Manji, global head of neuroscience drug development at Johnson & Johnson, predicted that brain researchers were on the cusp of a golden age.

That was before J&J's highly anticipated Alzheimer's drug, bapineuzumab, failed to improve memory and thinking skills in closely watched clinical trials of people with mild to moderate forms of the disease.

Had it worked, the drug would have been the first to alter the course of Alzheimer's, a fatal brain-wasting disease that affects 36 million people worldwide. It also would have meant billions of dollars in annual sales.

Instead, J&J and its partners, Pfizer and Elan, pulled the plug on the intravenous treatment after years of development.

Nevertheless, Manji, the Kenyan-born scientist who spent 15 years researching neuropsychiatric diseases for the National Institutes of Health, stands by his prediction.

The former chief of the NIH's Mood and Anxiety Disorders Program, who recently met with computer experts at NASA to understand how best to untangle the web of disparate information on brain science, says there is nothing more complex than brain disorders.

"We shouldn't expect it to be easy," Manji, 53, who leads the company's research efforts in Alzheimer's, mood disorders, schizophrenia and pain conditions, said in an interview.

Like its rivals, J&J is preparing to pivot from testing drugs in people who already have dementia to early-stage patients,

when drugs may have a better shot at working.

In November, J&J partnered with Japan's Shionogi to gain access to Shionogi's oral beta secretase, or BACE, inhibitor, a promising new class of drugs that aims to prevent the production of the Alzheimer's-linked protein beta amyloid before it can form toxic clumps in people's brains.

While J&J and its partners are retooling bapineuzumab into a more convenient shot formulation – instead of an IV – the company is also working on other approaches, including an amyloid-attacking antibody similar to bapineuzumab, called AAB003, and a vaccine that would enlist the help of an individual's immune system to fight the disease.

Manji says the company remains committed to amyloid-clearing treatments. He expects doctors will need a whole menu of drugs to address the massive burden of Alzheimer's, which is expected to affect 115 million people globally by 2050.

Earlier Treatment

Experts liken Alzheimer's to heart disease, in which fatty plaques build up in the arteries for years before breaking loose, causing a stroke or heart attack.

"If someone comes into the ER with a heart attack and you give them a (cholesterol-lowering) statin drug for the first time, you are probably 15 years too late," said Dr. Michael Rafii, an Alzheimer's expert at the University of California at San Diego.

Likewise, with Alzheimer's, when a patient enters the dementia phase, treatments that remove amyloid may be too little, too late. That may be what occurred with bapineuzumab, which showed signs that it was removing plaques but offered no cognitive benefit.

Late-stage studies of Eli Lilly and Co's similar drug,

solanezumab, also failed to help patients with mild-to-moderate Alzheimer's, but when the results of two studies were combined, researchers saw a hint of benefit in people with mild disease.

Many experts believe BACE inhibitors would be ideal for very early-stage patients because they may prevent dementia from developing.

Lilly and Merck already have midstage trials under way for their BACE inhibitors, with safety results expected by early 2014. J&J is still working out the details, but Manji said he expects human trials of the Shionogi drug to start soon.

Unlike anti-amyloid drugs, such as bapineuzumab, that remove plaque after it has formed, BACE inhibitors focus on preventing the production of beta amyloid. The drugs are designed to keep the enzyme beta-secretase from chopping up a larger protein called amyloid precursor protein (APP) into bits that make up beta amyloid.

A study published in July in the journal Nature helped fuel enthusiasm for BACE inhibitors. It found that people who have a mutation in APP are protected from Alzheimer's, and this gene affects the activity of BACE, suggesting that BACE inhibitors might work.

"It is almost like these people are born with natural BACE inhibition that seems to protect them," Manji said.

Developing a beta secretase inhibitor has presented a number of challenges, including understanding how to get the drugs across the protective blood-brain barrier and into the right spot in the brain. But after a decade of research, Manji says there is optimism that "the BACE nut has been cracked."

Manji said the challenge now is to block some of the enzyme's activity, without causing unintended side effects.

“What we still don’t completely know is if you get into enough people, are there some off-target effects you will discover?”

Other Avenues

To test new drugs in people with earlier-stage Alzheimer’s, scientists have organized a series of prevention trials, enrolling people who are genetically predisposed to develop Alzheimer’s or whose tests suggest they have pre-symptomatic disease.

Two Roche drugs, crenezumab and gantenerumab, and Lilly’s solanezumab and its BACE drug are among the first to be tested in these trials. No J&J drugs will be part in these early trials, but Manji says the company will benefit.

“I think the whole field is going to learn so much about the disease and the trajectory and the progression, irrespective of what compound is being used,” he said.

Meanwhile, J&J has provided seed funding for a pilot study in people with Down syndrome, another population that is predisposed to develop dementia early.

Manji is excited about efforts with partner Pfizer to develop a vaccine that targets amyloid. He says the vaccine, now in midstage trials, has overcome some of the issues that scuttled development of a similar effort by Elan in 2002.

Manji thinks the quickest way for drug companies to find answers to problems like Alzheimer’s will be through alliances to share information about underlying disease biology.

“If we are willing to stay the course and work together, we will make progress,” he said.