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BUSINESS DAY

Alzheimer's Drug LMTX Falters in Final Stage of Trials

By ANDREW POLLACK JULY 27, 2016

A new type of drug for Alzheimer's disease failed to slow the rate of decline in mental ability and daily functioning in its first large clinical trial. There was a hint, though, that it might be effective for certain patients.

The drug, called LMTX, is the first one with its mode of action — trying to undo so-called tau tangles in the brain — to reach the final stage of clinical trials. So the results of the study were eagerly awaited. The initial reaction to the outcome was disappointment, with perhaps a glimmer of hopefulness.

Over all, the patients who received LMTX, which was developed by TauRx Therapeutics, did not have a slower rate of decline in mental ability or daily functioning than those in the control group.

However, the drug did seem to work for the subset of patients — about 15 percent of those in the study — who took LMTX as their only therapy. The other 85 percent of patients took an existing Alzheimer's drug in addition to either LMTX or a placebo.

"There were highly significant, clinically meaningful, large effects in patients taking the drug as monotherapy, and no effect in patients taking it as an add-on," Claude Wischik, a founder and the chief executive of TauRx, said in an interview. He spoke from Toronto, where the results were being presented at the Alzheimer's

Association International Conference.

Dr. Wischik said a second clinical trial sponsored by the company, whose results will be announced later, found the same phenomenon. He said the company planned to apply for approval of LMTX to be used by itself.

But some experts not involved in the study were skeptical about drawing conclusions from a small subset of patients, especially since there was no obvious explanation why LMTX would be expected to work only in patients not getting other drugs. Regulators might also be skeptical and require the company to conduct another large study, this time only with participants not using other drugs.

"I have to say that the results that we saw here were, to me, more disappointing than not," Dr. David Knopman, a neurologist at the Mayo Clinic, said in moderating a news conference at the meeting in Toronto.

Dr. Rachelle Doody, director of the Alzheimer's disease and Memory Disorders Center at Baylor College of Medicine, agreed. "To present it to the public now as a promising approach seems unjustified," she said.

The Alzheimer's field is littered with unsuccessful experimental drugs. The handful of drugs that have reached the market, like Aricept and Namenda, temporarily affect symptoms but do not hit at the underlying mechanism of the disease.

Most efforts to modify the disease mechanism so far have tried to counter the buildup in the brain of beta-amyloid, a protein that forms sticky plaques.

Those drugs have not been successful. . But as with TauRx, some of the companies involved say there are signs the drugs work for certain patients, particularly those in a very early stage of the disease. So studies are continuing at Eli Lilly, Biogen, Roche and other companies.

Still, the failures of the amyloid drugs so far have prompted companies, including AbbVie, Biogen and Roche, to begin looking more at tau, another protein

in the brain. When it becomes abnormal, it aggregates into tangles that kill neurons and can spread through the brain. Some studies suggest that levels of tau are more closely correlated with cognitive decline than levels of amyloid.

"There is increasing evidence that tau is more proximal to the onset of disease symptoms," said William Jagust, professor of public health and neuroscience at the University of California, Berkeley.

The results of the LMTX trial do not necessarily spell doom for all tau drugs, because others might work differently. LMTX is "not the be-all and end-all for tau targeting," said Harry M. Tracy, publisher of NeuroPerspective, a newsletter that follows companies developing neurology drugs.

Dr. Wischik has been studying tau since his days as a doctoral student at Cambridge University in the 1980s. TauRx, which is privately held, operates out of Aberdeen, Scotland, and Singapore. Investors include Genting Berhad, a Malaysian investment company, and Temasek, a government-owned investment company in Singapore.

LMTX, which is TauRx's only drug, is a derivative of methylene blue, a dye. It is also being tested as a treatment for frontotemporal dementia, another neurodegenerative disease, with results expected next month.

TauRx's first clinical trial in Alzheimer's, announced in 2008, also had equivocal results. One dose slowed cognitive decline, but a higher dose had no effect. The company said there was a problem in the formulation of the higher dose. LMTX is a new formulation intended to avoid that problem.

The Phase 3 trial presented on Wednesday had 891 patients from 16 countries with mild or moderate Alzheimer's disease. They were randomly assigned to be treated with a lower dose of LMTX, a higher dose of LMTX or a placebo. (The placebo contained a tiny amount of LMTX to turn the patients' urine bluish green. Otherwise people would know if they were getting the drug or the placebo based on the color of their urine.)

The subset of patients taking LMTX but no other Alzheimer's drugs had essentially no decline in cognition or daily functioning for the entire 15 months of the trial, said Dr. Serge Gauthier, director of the Alzheimer's disease research unit at McGill University and the principal investigator of the trial. He is also chairman of TauRx's scientific advisory board.

The difference between those patients and the total population getting the placebo, who did decline, was about six points on a measure of cognition called ADAS-cog. That difference is considered clinically meaningful.

The rate of brain atrophy, as measured by M.R.I., was also slowed in those taking LMTX without other drugs. Dr. Gauthier said it was the first time a reduction in brain atrophy had been seen in a clinical trial of an Alzheimer's drug.

Side effects included nausea, diarrhea and urinary discomfort.

Dr. Wischik said the separate analysis of those not taking other drugs was planned in advance, not an after-the-fact "data dredging" exercise to come up with some positive sign.

He said one hypothesis why LMTX did not work with other drugs was that the other drugs set off a mechanism that cells use to expel drugs. LMTX was caught up in this and also expelled from brain cells. But this has yet to be proved.

It is possible that some other factor, not the drug, could explain why those patients did better. Such patients tended to be disproportionately from Eastern Europe and Malaysia, for example. The reported results compared the patients taking LMTX alone with the entire placebo group, not only the placebo patients getting no other Alzheimer's drugs, which would have been a more apt comparison.

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