NEWS

Controversial autism drug gets ambitious new trial

BY **NICHOLETTE ZELIADT**

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The makers of a drug designed to correct an enzyme shortage seen in some children with autism are testing the treatment in children with autism who do not have that deficiency. If the drug works in these children, it will come as a surprise to scientists who say the trial has no scientific basis.

The New York-based drug company **Curemark** developed the drug, known as CM-AT, for children with autism who have unusually low levels of chymotrypsin, an enzyme needed to break down dietary protein into amino acids the body cannot make on its own. The drug is a powdered blend of chymotrypsin and similar enzymes that parents sprinkle on their child's food. (Curemark representatives declined to identify any of the other components of the drug).

According to the company's scientific officers, the idea underlying the drug is this: Amino acids serve as building blocks for chemical messengers in the brain that some children with autism may lack. By releasing essential amino acids, CM-AT restores the necessary levels of these chemicals in the children's brains.

Joan Fallon, the company's chief executive officer, says the drug **improved irritability** in the participants of a trial **completed in 2011**. The trial included 182 children with autism who had low chymotrypsin levels. After 90 days of treatment, these children had become less socially withdrawn, Fallon says.

Outside experts have long been **skeptical of the therapy's premise**. Their reason: Curemark has yet to publish any of the results. The fact that the company is testing the treatment in children who don't match the original rationale is leaving experts even more nonplussed.

"If [the children] have normal chymotrypsin levels, why do they need extra?" says **Mark Corkins**, pediatric gastroenterologist and professor of pediatrics at the University of Tennessee in Memphis. "I'm scratching my head; it doesn't make sense to me."

Curemark officials say the new trial's scope was not their idea, but rather a directive from the U.S. Food and Drug Administration (FDA). The company submitted its data to the agency as soon as the 2011 trial was complete, says chief scientific officer **Matthew Heil**. He says the FDA then asked Curemark to include children with autism who have normal levels of chymotrypsin.

"That was surprising to us," Heil says. "That was not part of our original design or desire."

Heil says the FDA wanted this information so they could pin down the wording on the drug's label. If it doesn't work in children with typical chymotrypsin levels, the drug's label would reflect that limitation.

A spokeswoman for the FDA declined to confirm Heil's account, saying the agency does not reveal information about drugs in trials.

Under scrutiny:

In the scientific community, access to details about how the drug works or the previous trial would go a long way toward easing the skepticism.

"I would be very cautious when someone's been talking about profound efficacy data for, what, five years now, and has never shared any of it," says **Randall Carpenter**, chief scientific officer of the Rett Syndrome Research Trust, a Connecticut-based nonprofit organization.

Curemark officials say they have submitted an abstract to present their data next May at the **International Meeting for Autism Research**. They say they were waiting to present any data publicly until they had approval from the FDA.

Curemark began recruiting participants for its new trial in May 2015. Fallon says the company **aims to enroll** at least 300 children with autism, aged 3 to 8 years, across 30 sites in the United States. According to the study design, the participants receive a sprinkle of either CM-AT or a placebo powder on their food three times a day for 90 days. None of the children, their parents or the investigators know whether a child gets the placebo or the drug.

The researchers assess behavioral changes in the children every two weeks via a parent questionnaire called the Aberrant Behavior Checklist (ABC). They focus primarily on two parts of this checklist: one that measures irritability and agitation, and another that gauges lethargy and social withdrawal. They used the same measures in the previous CM-AT trial. Trials to evaluate risperidone and aripiprazole, the only two drugs approved for autism, also relied on this questionnaire.

Heil says the company does not expect to see behavioral improvements in children who have typical levels of chymotrypsin. "I would be very surprised if we found out that absolutely everybody

benefits," he says.

Treatment tracking:

Experts say it is important for the company to track whether the drug works the way it is proposed to. For example, if CM-AT boosts protein digestion, then it should up the levels of amino acids in a child's bloodstream. "Show me that those change," Corkins says.

Fallon says the trial's researchers are not collecting those data in the trial, but are monitoring the children for any digestive problems, such as constipation or diarrhea.

At the least, the treatment is unlikely to be harmful, because the body naturally makes digestive enzymes, Corkins says. "A replacement enzyme, in theory, is probably a very safe thing."

Still, the trial diverts resources away from potentially more worthwhile efforts, says **Katrina Williams**, professor of clinical sciences at the Murdoch Children's Research Institute in Victoria, Australia.

"Is there something that might have been a better use of that level of organization in a trial?" she says. There is an "opportunity cost," she says, from spending time and money investigating CM-AT in lieu of options with better evidence backing them.