

HEALTH

Merck Plans to Start Phase II Of AIDS-Vaccine Human Trials

Scientists to Test Prototype Deemed Most Promising For Safety, Effectiveness

By **MARILYN CHASE**

Merck & Co. said it is launching the second phase of human trials on an AIDS vaccine that scientists called the most promising of its kind.

The prototype AIDS vaccine will be tested in 1,500 people in the U.S., Canada, Australia, Latin America and the Caribbean.

The Phase II clinical trial will evaluate safety and effectiveness of the vaccine. The trial is a collaboration between Merck, the HIV Vaccine Trials Network and the National Institute of Allergy and Infectious Diseases, a unit of the U.S. National Institutes of Health.

The Merck trial joins approximately 50 other AIDS vaccine trials in progress, all with the hope of halting the epidemic disease that affects about 40 million people and killed 3.1 million in 2004.

Labeled MRKA5, the vaccine uses an adenovirus—a common virus that causes colds—as a missile armed with man-made copies of three genes taken from the inner core of the AIDS virus. Researchers hope these three genes will spark killer cells, known as cytotoxic T-cells, to destroy human cells infected by HIV, the human immune-deficiency virus that causes AIDS.

"It's an exciting trial conceptually," said Lawrence Corey, principal investigator of the HIV Vaccine Trials Network. Compared with other vaccines aimed at marshaling killer T-cells, MRKA5 has "given the best immune response," he

said. Dr. Corey said he receives no stock or personal funding from Merck.

This study will compare the response of volunteers given three injections of the vaccine over six months against a control group given dummy injections. The study is expected to last at least 4½ years, and will examine infection rates, as well as severity of disease in the two groups. All participants will be instructed in safe sex and other preventive behaviors.

An ideal vaccine would fight HIV two ways, by blocking infection in the first place, and fighting any virus that sneaks in. Merck's experimental vaccine, however, doesn't contain the gene for the virus's outer coat, a component that would be needed to spark neutralizing antibodies that would bar any initial infection. Still, the researchers are hoping that marshaling the killer T-cells would be enough protection, by virtue of destroying infected cells once the AIDS virus gets inside, to at least prevent or delay onset of the disease.

Based on a prior Phase I safety study of this vaccine in 250 people, the company and researchers said they believe that MRKA5 is safe. Some volunteers developed fevers and muscle aches that resolved in 48 hours.

This vaccine contains genes from the AIDS virus strain that predominates in North and South America. Any successful AIDS vaccine ideally would include HIV types found all over the world.

"Nobody," Dr. Corey said, "has given up on developing a global HIV vaccine."

Robert Belshe, professor of medicine at Saint Louis University in Missouri, one of the testing sites, said he is optimistic because this vaccine prevented or delayed the onset of AIDS-like disease in animals. "This is a step forward. It's clearly not the final vaccine. We still need antibodies. This is half the equation," he said.

Aches & Claims / By *Reed Albergotti*

Auditory-Feedback Device May Help Stutterers

Devices that fit into the ears of stutterers to help them speak more smoothly have been getting attention in the world of speech pathology. While they are instantly effective for some stutterers, they have no effect on others, and a lack of research has left scientists wondering why.

* * *

One device, called the SpeechEasy, fits into the ear like a hearing aid. A tiny microphone picks up the user's voice and then plays it back into the ear at a different pitch. Essentially, users hear a computer-generated, modified echo. It is similar to what is sometimes heard on a bad cellphone connection. But what is an annoyance to typical speakers somehow can smooth the speech of someone with the disorder.

Scientists don't fully understand the phenomenon. Some scientists link it to the "choral effect," in which most stutterers speak fluently while singing in a choir or reading

out loud in unison with a group. Because stuttering is widely believed to be a neurological problem, and not a hearing or emotional problem, experts say the feedback alters the neurological process somewhere along the line, in a way that helps some and does nothing for others.

Forms of delayed auditory feedback, a technology the SpeechEasy employs, were first used to treat stuttering as far back as 50 years ago. But technology limited it to the speech-therapy lab, where patients put on headphones, spoke into a microphone and used a computer the size of a large tape recorder. Whether it helped once the patient left the lab hasn't been proved.

Now that it is available in the form of a small, inconspicuous device in the ear, the delayed feedback method is being examined more as a possible solution to stuttering. A handful of new academic studies are being conducted on users of the SpeechEasy device, which came out more than three years ago, and some preliminary results are already trickling in.



Tim Foley

Speech pathologists, though, have found the effect of the device can wear off in some patients over time because the mind can adapt to the distraction in the ear. And other patients find the echo too annoying to deal with, especially because the device echoes ambient sound as well. Some patients remove or turn it off during the normal course of the day, but activate it for speeches, presentations or important conversations.

The device carries a hefty \$4,000-\$5,000 price tag, which usually

isn't covered by health insurance. Janus Development Group Inc., which makes the device under a distribution license from East Carolina University, offers a 60-day money-back guarantee of 90% of the product's cost. Of the 4,500-5,000 it has sold, it says about 10% have been returned.

To determine whether SpeechEasy is right for a person, speech therapists conduct a three-hour test, fitting the device, hooking it up to a computer and experimenting with the length of the delay as well as the pitch. For some patients, it works off for a little while and then wears off by the end of the session.

Most speech therapists don't recommend the device for children, who can benefit more from speech therapy at a young age. Most children who stutter shake the problem in adulthood.

Adults who stutter should check state vocational rehabilitation offices, which sometimes chip in for speech therapy or devices like the SpeechEasy. They can get information from the Stuttering Foundation of America at www.stutteringhelp.org.

Send e-mail to Aches@wsj.com

Study by Vioxx Critic Links Drug to Extra Coronary Cases

By **JEANNE WHALEN**

Merck & Co.'s arthritis drug Vioxx may have caused as many as 140,000 excess cases of serious coronary heart disease in the U.S. by the time it was withdrawn from the market in September, an FDA official and several fellow scientists conclude in a study to be published in a medical journal today.

Many of these cases of heart disease may have been fatal, David Graham, associate director for science in the U.S. Food and Drug Administration's Office of Drug Safety, writes in the Lancet. Dr. Graham, an outspoken critic of Vioxx and other anti-inflammatory drugs, has made public some of his Vioxx data in recent months but hasn't published it in full until now.

His findings will likely raise the volume on the drug-safety debate that has swept Washington in recent months. Dr. Graham and other critics of the FDA accuse the agency of being too slow to ban or tighten regulations on medicines that cause serious side effects.

A Merck spokesman said the estimate of harm from Vioxx was "speculation." The study that prompted the company to withdraw the drug showed an increase in heart attacks and strokes only after 18 months, and no difference in the rates of fatalities between people taking Vioxx and people taking a placebo pill, he said. Determinations of Vioxx's potential role in patients' cardiovascular problems "can only be made on a case by case basis," he said.

When Merck withdrew Vioxx in the fall, the company said a study had shown that people who took Vioxx for more than 18 months were twice as likely to have a heart attack or stroke as those taking a placebo.

Dr. Graham's study compares the incidence of coronary heart disease in patients taking Vioxx and other anti-inflammatory drugs. The study analyzed data from 1.4 million patients taking such drugs in California from 1999 to 2004. People taking Vioxx had a 34% higher chance of coronary heart disease when compared with people who used other anti-inflammatory drugs, the study concludes.

In a phone interview, Dr. Graham said he had intended to publish the study in the Lancet last November but withdrew the article at the last minute under pressure from an FDA official. Dr. Graham said the official wrote him an e-mail warning that there would be "serious adverse consequences" for him if the article was published. Dr. Graham declined to provide a copy of the e-mail. The Lancet's editor didn't respond to a request for comment.

FDA officials have disputed Dr. Graham's critique of the agency's handling of safety matters, and have said they don't retaliate against scientists who disagree with their superiors.

Some of Dr. Graham's data have

changed over time. His study focused on the risk of heart attacks and sudden cardiac deaths, comparing patients who had taken anti-inflammatory drugs with patients who hadn't taken any painkiller for at least 60 days. In a paper Dr. Graham presented at a conference last August, he concluded that patients who had taken doses of Vioxx higher than 25 milligrams a day were 3.15 times as likely to have a heart problem. In the Lancet paper, the 3.15 changes to a ratio of 3. Dr. Graham said the difference arose when he removed 1,356 patients from the study that he determined were ineligible. But he added that "substantively, the conclusions are identical" in the August paper and Lancet publication.

Vioxx belongs to a group of drugs known as Cox-2 inhibitors. Also yesterday, the consumer group Public Citizen asked the FDA to remove the two remaining drugs in the class, Pfizer Inc.'s Bextra and Celebrex, from the U.S. market. A spokeswoman for Pfizer said in a statement that the company "remains confident in its Cox-2 medicines as important treatment options that provide necessary pain relief for patients around the world" and the advisory committee meeting is an "appropriate setting" for discussing the drugs.

An FDA spokeswoman said the agency will "review the petition carefully." An FDA advisory committee is set to examine Cox-2 drugs and other painkillers in February.

—Anna Wilde Mathews contributed to this article.

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Bird-Flu Cases Likely Transmitted by Girl

A WALL STREET JOURNAL NEWS ROUNDUP
 Medical sleuths puzzling over three related bird-flu cases in Thailand last year now strongly believe that two women who cared for a sick child both caught the virus from the girl, according to a study.

An international team of scientists led by the Public Health Ministry in Thailand believes that an 11-year-old Thai girl became ill with the virus last September and probably passed it on to her mother and aunt. The girl and the mother died 12 days apart. The aunt survived.

World health experts previously theorized that the girl passed the H5N1 virus on only to her mother and that it was a dead-end case. This is the first time scientists have said the aunt also probably caught the virus from the child. But they have found no evidence of the virus mutating.



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