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Cardiologists Question Delay of Data on 2 Drugs

By ALEX BERENSON

Prescriptions for the cholesterol-lowering drugs Zetia and Vytorin are written for almost 800,000 Americans every week, at a cost this year of about \$4 billion. Yet it still is not clear how well the drugs work.

Nearly two years after the medicines' makers, Merck and Schering-Plough, completed a clinical trial of the drugs, they still have not released the findings. The delay has led to a growing chorus of complaints from cardiologists. And yesterday, the companies responded by promising to publish a portion of the results next March — but not the entire set of data.

Doctors say that decision is highly unusual and will do little to quell concerns about the trial, as well as broader questions about the effectiveness of the drugs.

Cardiologists have been awaiting the results of the trial, called Enhance, to learn how well Zetia and Vytorin work. If they are not as effective as other cholesterol medicines, patients taking them may be putting themselves at unnecessary risk of heart attacks.

"There's clearly some rightful interest in what the results are," said Dr. Allen J. Taylor, chief of cardiology at Walter Reed Army Medical Center. "You've got millions of people treated with the drugs."

Whatever its results, the trial will not answer all questions about Zetia and Vytorin, either positively or negatively. Those answers may have to wait for a bigger study that will not be completed until at least 2010. But with so many patients taking the drugs, cardiologists are looking for whatever information they can get.

The delay in publishing the Enhance results also raises broad questions about whether the drug industry is sticking to its promises to improve the disclosure of clinical trials. After sharp criticism for failing to disclose trials that had negative results, drug makers promised two years ago to publicly register clinical trials in advance and promptly disclose their findings. But in practice they face few penalties for failing to meet those promises.

Of particular concern in this case is that Merck and Schering-Plough said yesterday that they had changed the trial's "primary endpoint" — the main medical result being measured. The companies now say that they will use only partial results to assess the trial's success in deterring the formation of plaque that can cause artery blockages and lead to heart attacks.

Merck and Schering-Plough say that the change is appropriate and will enable them to finish their work in time to present the trial's results in March, at the American College of Cardiology annual conference in Chicago.

But scientists generally assume that for a clinical trial to be valid, its goals must be defined before it begins and never changed afterward. Otherwise, the people conducting the trial could change their goals to conform to the data the trial has actually produced.

"This sounds highly unusual to me," said Dr. Bruce Psaty, a professor of medicine and epidemiology at the University of Washington. "You need to live with your primary endpoint."

Another big drug maker, Pfizer, for example, was harshly criticized in 2001 for reporting that its painkiller Celebrex caused fewer ulcers than older drugs after six months of use. Pfizer's study had originally been designed — but failed — to show that Celebrex caused fewer ulcers after a full year of use.

Yesterday, Merck and Schering said they did not yet know the results of the trial. They said they were changing the endpoint only because they want to be able to analyze the data more quickly.

A panel of outside scientists recommended the change last Friday, said Lee Davies, a spokesman for Schering. Mr. Davies declined to disclose the members of the panel.

Dr. Howard Weintraub, the clinical director of the New York University center for the prevention of cardiovascular disease, said cardiologists were especially concerned about the trial's results because Zetia works differently from other cholesterol-lowering medicines like Lipitor or Merck's own Zocor.

Unlike the other medicines, called statins, Zetia has not yet been proven to prevent heart attacks. The Food and Drug Administration approved it in 2002 on the basis of trials that showed it could lower LDL, or so-called bad cholesterol, by 15 to 20 percent.

Zetia is the brand name for a cholesterol-lowering medicine called ezetimibe. It can be taken with any statin. Vytorin is a single pill that combines Zetia with simvastatin, the active

ingredient in Merck's Zocor statin.

Together, Zetia and Vytorin have grabbed nearly 20 percent of the American market for cholesterol-lowering drugs, because of aggressive marketing from Merck and Schering-Plough that highlights Zetia's uniqueness among cholesterol medicines.

Because Zetia's cholesterol-lowering effect comes on top of that produced by statins, doctors often prescribe the drug in combination with low-dose statins, as an alternative to increasing the statin dose. Some patients do not like taking high-dose statins because they can cause muscle pain.

Merck's Zocor is now subject to cheap competition from generic simvastatin that costs pennies a day. But Merck can continue to command name-brand prices through Zetia and Vytorin, which both cost about \$3 a day, similar to other branded cholesterol-lowering drugs like Lipitor.

Merck and Schering co-market Zetia and Vytorin and split revenues and profits roughly equally.

Despite the success of the marketing campaign, some cardiologists say they are concerned that reducing cholesterol through Zetia may not protect the cardiovascular system as much as reducing it through a statin.

"Cholesterol lowering with this drug might not provide the same benefits as statins for the same degree of cholesterol reduction," said Dr. Steven Nissen, the chairman of cardiovascular medicine at the Cleveland Clinic.

The Enhance trial was supposed to end those questions. It was intended to show that Zetia and simvastatin would reduce the growth of plaque in blood vessel walls more than simvastatin alone — an important measure of the effectiveness of cholesterol-lowering medicines.

The companies had said they would measure the thickness of plaque in two arteries — the carotid, which runs through the neck and supplies the brain with blood, and the femoral, which runs through the hips and supplies the legs. The primary endpoint of the trial was supposed to be the amount of plaque at three points in the carotid artery.

But the companies said yesterday that they had changed the primary endpoint to measuring thickness at just one place in the carotid. And they do not expect to release any results at all from the femoral artery.

Dr. John Kastelein, the Dutch cardiologist who oversaw the Enhance trial, said he believed that the trial should still be considered valid. The single carotid endpoint is still an important measure of the drug's effectiveness, he said.

The Zetia-Vytorin dispute adds to the controversy that has engulfed the field of medical clinical trials. After being criticized for hiding negative trials, the industry promised to improve disclosure by listing most new trials at their outset on a federally financed Web registry. A separate registry, run by an industry lobbying group, is supposed to provide a place for companies to post the results of trials shortly after their completion.

But the still-unreleased data from the Enhance trial indicates the limits of the system, doctors say. Companies do not face meaningful penalties for failing to post results, and they can delay disclosure for years by saying that they are still analyzing data.

The Enhance trial, which involved 720 patients with very high cholesterol, began in June 2002. In June 2006, a Schering executive told investors that the Enhance data would be ready by year-end, although it might not be publicly presented until 2007. At the latest, doctors had expected the results by the American College of Cardiology conference in March 2007.

In an interview yesterday morning, Dr. Kastelein, the study's leader, said he had hoped to present the results of the trial at the March 2007 conference. But Schering and Merck controlled the raw data and raised questions about its accuracy, resulting in long delays, he said.

"There was friction and tension," he said. But he added that he did not believe the companies had manipulated the data.

The delays in the Enhance results stand in sharp contrast to a similar trial conducted by AstraZeneca on its cholesterol-lowering drug Crestor. That trial, called Meteor, compared Crestor to a placebo in patients with moderately high cholesterol and also involved measuring plaque.

It was completed in May 2006, and the results were released 10 months later, showing positive results for Crestor. Dr. John R. Crouse, a Wake Forest University professor who oversaw the AstraZeneca trial, said he knew the Crestor's trial's findings by September 2006.

Still, Dr. Crouse said that measuring plaque can be complicated and that Merck and Schering might simply have run into delays in analyzing their data. "It's easy for things not to go the way you would hope they would go," he said.

Some other cardiologists are less willing to wait for Merck and Schering to finish their analysis.

“Statins have diverse effects beyond simple LDL cholesterol lowering, such as potent anti-inflammatory actions,” said Dr. Eric J. Topol, a cardiologist and director of the Scripps Translational Science Institute in La Jolla, Calif. Referring to Zetia, he said, “There has yet to be a clinical trial to show that ezetimibe improves clinical outcomes.”

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