

Re: Merck, Schering–Plough Defend Efforts for Vytorin, Zetia

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New Vytorin Report Draws Fire
Matthew Herper, 01.25.08, 3:25 PM ET

For the first time, Merck and Schering–Plough have released details of how a key study of their cholesterol drug Zetia, also used in the combo pill Vytorin, wound up being delayed for more than a year after its findings were originally expected. But the report has inflamed critics rather than pacified them.

"I think it's great they're disclosing this," says Harlan Krumholz, a cardiologist at Yale University. "I think there's nothing here that's reassuring. It raises more concerns."

At best, Krumholz and others claim the companies bungled the research; at worst, they say Merck and Schering–Plough may have deliberately stalled revelations that the \$5 billion cholesterol franchise did no better than a cheap generic.

Committees from both houses of Congress are investigating the delay, and the companies gave a similar version of the same timeline to the House Committee on Energy and Commerce Thursday.

The company defended its actions: "While the ENHANCE trial was time–consuming and took longer than [we had] originally anticipated to complete, our companies acted with integrity and good faith in connection with the trial," said Thomas Koestler, who heads research at Schering–Plough, in a prepared statement.

Since revealing that Vytorin failed to reduce atherosclerosis better than the cheap generic Zocor, shares of both companies have fallen. Schering shares are down 25%, Merck shares 15%. The companies split profits from Zetia and Vytorin 50–50, through a joint venture that markets both pills.

In the five–page timeline released Friday, the companies say Schering–Plough biostatisticians first became concerned about the data by the end of 2005. These statisticians became aware of instances of what the companies called "biologically implausible" data. Those concerns led

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the company to bring in outside consultants at least a half–dozen times, to look at the ultrasound pictures of arteries being generated by the trial, and to deal with problematic or missing images.

But at least one of the companies' outside experts said Friday that the data quality of the study was similar to that of other trials. Still, the companies did even more analyses of the database, and say they did not actually begin the process of "unblinding" the data until Dec. 31, 2007. On Jan. 14, the companies issued the press release detailing the long–awaited results of the study.

Krumholz still worries the delays could well have been caused by commercial—not scientific—concerns. "By the summer of 2005, their marketing division is so successful that it already is a blockbuster drug. There was only downside [to analyzing the results.]"

Allen J. Taylor, head of cardiology at Walter Reed Army Medical Center, says that, based on the release, "the fundamental question does remain at which point they knew the study did not favor one group over the other."

Moreover, he says, spending so long trying to clean up the data was not appropriate in any case. "It's not liking the answer and hoping that if you do it again you'll get a better answer," says Taylor. "The fact they never found a good solution validates the point: The data are the data."

In an interview Friday, John Kastelein of the University of Amsterdam, the lead outside scientist conducting the trial, says he was not consulted about the timeline or the press release before it was issued. "If people want to really judge the quality of this trial, they should wait until the data were peer–reviewed," he says. At that point, they will be presented at a medical meeting or in a medical journal.

Meanwhile, the American College of Cardiology, which had earlier issued a statement warning that patients and physicians should not draw too many conclusions from the study, issued a second statement Friday clarifying that Zetia and the Vytorin combo pill should be used only after other medicines with more evidence of benefit have been tried.

Douglas Weaver, chief of cardiology at Henry Ford Hospital in Detroit and president–elect of the ACC, says that the new statement came partly as a response to full–page advertisements from Merck and Schering defending Zetia and Vytorin and telling patients not to overreact to the ENHANCE study's findings.

"It's concerning to us, because we're worried that patients who really aren't experts and read this casually could interpret that the ACC endorse this as a first–line therapy," says Weaver. "We do not want to

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be seen as doing that. I'm kind of surprised the companies did that."