United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

http://finance.senate.gov
Press_Office@finance-rep.senate.gov

M E M O R A N D U M

TO: Reporters and Editors
FR: Jill Kozeny, 202/224-1308
for U.S. Senator Chuck Grassley of Iowa
RE: the Vytorin study
DA: March 31, 2008

Through his review of the delayed release by Merck/Schering Plough of results from the ENHANCE trial, Senator Chuck Grassley has discovered that the companies budgeted approximately $3.5 million for a six-week public relations blitz called the "49 Plan," which was designed to get doctors to switch patients to Vytorin from cheaper statins. Senator Grassley also has learned that the lead researcher of the ENHANCE trial indicated that the companies may have delayed the publication of trial results for marketing purposes.

These new findings of Senator Grassley's are described in a letter sent today to Merck & Co. and Schering-Plough Corporation. Yesterday, the drug makers released the long-awaited results of the ENHANCE trial during a meeting of the American College of Cardiology. Separately, Senator Grassley also sent a letter today to the American College of Cardiology regarding contributions to the organization from these drug makers.

Senator Grassley's comment:

"When a company bills the federal government hundreds of millions of dollars for a single drug, then it's important for the government to know how the drug works and that the therapy is cost-effective. At this time, experts are calling upon physicians to return to cheaper statins and await the finding of future studies."

Senator Grassley's letters sent today:

March 31, 2008

Richard T. Clark
Chairman, President, and Chief Executive Officer
Merck & Co. Inc.
1 Merck Drive

Whitehouse Station, NJ 08889

Fred Hassan
Chairman and Chief Executive Officer
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Messrs. Clark and Hassan:

As Ranking Member of the United States Senate Committee on Finance (Committee), I have an obligation to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to ensure that taxpayer and beneficiary dollars are spent in a fiscally sound manner. This includes the responsibility to conduct oversight of the medical and pharmaceutical industries to ensure that Medicare and Medicaid dollars are spent appropriately on safe and effective drugs and devices.

I continue to be troubled by reports that Merck and Schering Plough (M/SP) were delaying results of the ENHANCE trial. This study examined whether Vytorin provides better health benefits than generic simvastatin-a drug that is far less expensive than Vytorin. The ENHANCE trial was completed in April 2006, but the results were not released for almost two years.

I am pleased to see that M/SP finally released the long awaited results of the ENHANCE trial at this weekend's American College of Cardiology (ACC) meeting. However, I am troubled to learn that after careful analysis of the ENHANCE results, medical experts are now calling Vytorin the cholesterol fighter of last resort. According to reports today on CNBC, at least one prominent cardiologist is now referring to Vytorin as an "expensive placebo." Medical professionals should have had the facts about Vytorin much earlier so they could make informed decisions about the care that they provide to patients.

Delaying the release of the results from the ENHANCE trial not only affected medical decisions, but also imposed financial burdens on patients as well as the federal government. Since the ENHANCE trial was completed in 2006, the federal government has paid M/SP hundreds of millions of dollars for Vytorin.

Additionally, I am not the only one troubled by the delay in the release of ENHANCE. During their review of documents submitted by M/SP, my Committee staff found emails between Schering Plough employees and Dr. John Kastelein, the primary investigator of the ENHANCE trial. Those emails are seminal in documenting Dr. Kastelein's concerns about M/SP's delay in releasing the results of ENHANCE. Last July, Dr. Kastelein wrote to a Schering Plough executive:

Is it correct that SP has decided not to present at AHA, but to await the two other, completely unvalidated, endpoints, which analysis is going to take us straight into 2008??!!??

If this is true, SP must have taken this decision without even the semblance of decency to consult me as PI of the study. I can tell you that if this is the case, our collaboration is over… This starts smelling like extending the publication for no other [than] political reasons and I cannot live with that. 1

That next day, Dr. Kastelein wrote again to a Schering Plough executive:

I have been travelling half the globe in the last 6 months to a number of large and important meetings at the strong wish of Merck to chair them or to present ezetimibe data. At every single one of them I was cleared to say that ENHANCE would be presented at AHA.

There is no reason whatsoever to include femorals; you will be seen as a company that tries to hide something and I will be perceived as being in bed with you! 2

I am also troubled that M/SP may be placing marketing interests above science. For instance, in an M/SP marketing review done just last December, it appears that advancing sales, not science, was the priority.3 Page 8 of the document details messaging adjustments for 2008 such as "Incorporate 'lower is better' into message flow" and "incorporate switch message - SNAG (simvastatin not at goal). Another slide show created by your respective companies last year noted that, "History has shown that ZETIA is extremely sensitive to promotion, with consistent share growth demonstrated when fully promoted." 4

Further, it was reported in the media that M/SP launched an ongoing Public Relations blitz called the "49 plan," designed to wine and dine doctors and convince them to prescribe Vytorin. 5 In recent days, I have learned that M/SP budgeted at least $3.5 million for the "49 plan." This seems like a great deal of money for free lunches and dinners.

In addition, while the health benefits of Vytorin appear similar to a cheaper generic, the difference in cost to the patient and to the Medicare and Medicaid programs is significant. For instance, at a Wal-Mart pharmacy in Iowa City, generic simvastatin costs $54.54 for a month's supply. On the other hand, Vytorin costs $112.46-more than twice as much. Thus, I remain troubled that M/SP failed to report any results from the ENHANCE trial until January 2008 while trying over the last year or two to get doctors to switch their patients to Vytorin from other, less expensive statin drugs.

Accordingly, I request that M/SP respond to the following questions and requests for documents. In answering, please repeat the question and follow each question with the appropriate response and documentation as requested.

1. Please provide the names and titles of all Key Opinion Leaders (KOL) for ENHANCE, Vytorin, and/or Zetia.

2. Please provide a list of all payments, if any, made to these KOLs during the period of November 2007 to the present. For each payment to a KOL provide the following:

a) Name of physician

b) Date of payment
c) Payment description (CME, honorarium, research support, etc.)
d) Amount of payment

3. In addition to the $3.5 million budgeted for the "49 plan," how much was budgeted for the marketing and advertising of Vytorin since the ENHANCE trial was completed in April 2006, including direct-to-consumer advertising?

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

I look forward to hearing from you by no later than April 14, 2008.

Sincerely,

Chuck Grassley
United States Senator
Ranking Member, Committee on Finance

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1 Email from J.J.P. Kastelein to John Strony, cc: Enrico Veltri, dated July 6, 2007.
2 Email from J.J.P. Kastelein to John Strony, dated July 7, 2007.
3 Internal marketing document, Merck/Schering Plough Pharmaceuticals WWOC Review, dated December 17, 2007.
4 Internal Merck/Schering Plough document, "METEOR: Field Response Teleconference," dated March 26, 2007.
5 "49 plan": Ed Silverman "Schering-Plough Wines & Dines Zetia Docs," Pharmalot, March 11, 2008.

March 31, 2008

James T. Dove, M.D., F.A.C.C.
President
American College of Cardiology
2400 N Street, NW
Washington, DC 20037

Dear Dr. Dove:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under these programs. As Ranking Member of the Committee, I have a duty to protect the health of Medicare and Medicaid beneficiaries and safeguard taxpayer dollars authorized by Congress for these programs.

Last January, I sent you a letter because I was concerned about the supportive tone of the American College of Cardiology's (ACC) press release regarding the Merck/Schering Plough's ENHANCE trial. My concern stemmed from several newspaper reports which note that pharmaceutical companies provide monies to non-profit organizations in an attempt to influence their behavior. In response, several of your officials met with Committee staff members to explain ACC's policies on corporate donations and conflicts of interest.

First and most importantly, I appreciate your attention to this matter. I was happy to learn that ACC has firm policies in place to guard against undue influence from industry and to protect the organization's independence. However, I am a firm believer in transparency and I would like to inform you about some facts that I have uncovered.

Shortly after ACC sent out its press release on ENHANCE, Merck/Schering Plough officials began forwarding that press release internally, praising the ACC's support of Vytorin.1 In particular, one M/SP official wrote in an email dated January 16, 2008, "Further to my note below and my additional commentary on securing and aligning [Medical Science Liaisons] as credible supporters of the VYTORIN brand, please add to our armoury The American College of Cardiology (ACC)." (Emphasis added). That official then advised his colleagues to direct Merck/Schering Plough medical science liaisons to the ACC press release.

While I realize and appreciate the fact that ACC has policies in place to guard against conflicts of interest, I still have concerns that monies from Merck and Schering Plough create the appearance of influence. This is the case despite the fact that only a small portion of ACC's funds come from industry. Since 2003, Merck and its various foundations and divisions have donated almost $5M to ACC. This money has paid for conference booths, expo fees, educational seminars, and satellite event fees. Some of these payments included the following:

2008
$25,000 Promotional Banner Set (Januvia)
$50,000 Hotel "Do Not Disturb" Door Hangers
$192,000 6400 Sq Ft Booth Space
$270,000 HDL Education Initiative
$25,000 Two Promotional Banners - Cozaar
$6,150 ACC 2007 Scientific Sessions Dr. Bag

2004
$60,000 Cups

2003
$60,000 Insulated Cups
$5000 Cardiology at Cancun
$50,000 Cardiology Hypertension Track

In addition to Merck, Schering-Plough has separately made payments to ACC. Since 2003, Schering-Plough has given ACC more than $1M. This money included $50,000 for a

"premium satellite symposium" to be hosted during the ACC conference that took place this past weekend. Some of the other monies paid for the following:

2007
$634,000 Fund ACTION Registry
$15,000 Premium Breakfast Satellite Symposium

In addition to the monies paid separately by Merck and Schering Plough, ACC received more than $5M from the joint venture of Merck/Schering Plough Pharmaceuticals. This money paid for a variety of seminars and advertising on cardiology, Vytorin and Zetia, including $165,000 for a 5500 sq foot booth in 2008. Apparently, this was the booth for the ACC conference that took place just a few days ago.

I appreciate ACC's efforts to guard against undue influence from outside companies, but in light of the events surrounding Vytorin and ENHANCE, I am sure you can see why my concerns remain. It would not be unreasonable for an independent third party to conclude that the Merck and Schering Plough payments to ACC influenced ACC's comments about Vytorin, especially now that experts are calling for doctors to use this drug only as a last resort. I hope that you continue to vigorously guard against corporate influence to ensure that ACC remains independent.

Thank you for your attention to this matter.

Sincerely,

Chuck Grassley
United States Senator
Ranking Member, Committee on Finance

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1 Internal Merck/Schering Plough email

From: NAME REDACTED
Sent: Wednesday, January 16, 2008 1:49 PM
To: NAMES REDACTED
Cc: NAMES REDACTED
Subject: ACC and ENHANCE
Importance: High

Communications Colleagues,

Further to my note below and my additional commentary on securing and aligning MSLs as credible supporters of the VYTORIN brand, please add to our armoury The American College of Cardiology (ACC).

I suggest that your future media responses cite the following key points of the full text and link below:

http://www.acc.org/enhance.htm

1. The ACC recommends that major clinical decisions NOT be made on the basis of the ENHANCE study alone.

2. In ENHANCE:

(i) The overall incidence rates of cardiac events were nearly identical between both treatment groups

(ii) both medicines were generally well tolerated.

3. There should no be reason for patients to panic.

(i) Health care professionals should speak to their concerned patients using this drug.

(ii) This is not an urgent situation and patients should never stop taking any prescribed medications without first discussing the issue with their health care professional.

4. VYTORIN remains a reasonable option for patients who:

(i) Are currently on a high dose statin but have not reached their goal.

(ii) Cannot tolerate statins or can only tolerate a low dose statin.

I also recommend that these messages and the full text from the link be circulated to your aligned MSL spokespeople.

2 American College of Cardiology Foundation as of 2/11/2008

Senator Grassley's previous statements and letters:

M E M O R A N D U M

TO: Reporters and Editors
FR: Jill Kozeny, 202/224-1308
for U.S. Senator Chuck Grassley of Iowa
RE: Questions about statements regarding drug trial
DA: Tuesday, February 12, 2008

Senator Grassley is continuing his inquiries related to Schering-Plough's drug Vytorin and has asked for documents and a list of all company statisticians who had access to the ENHANCE trial data. The ENHANCE trial was an attempt to determine if Vytorin, a combination pill of Zetia and a statin, performed better than a generic statin alone. Senator Grassley has expressed concern that individuals who had early access to this data could have learned that Vytorin did not offer more value than an inexpensive statin. The ENHANCE trial ended in April 2006, but the results were not released until almost two years later on January 14, 2008.

Here is the text of his February 11 letter to the Schering-Plough Corporation.

February 11, 2008

Via Electronic Transmission

Mr. Fred Hassan
Chairman of the Board, Chief Executive Officer
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Mr. Hassan:

As the Ranking Member of the United States Senate Committee on Finance (Committee), I have an obligation to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to ensure that taxpayer and beneficiary dollars are spent in a fiscally sound manner. This also includes the responsibility to conduct oversight of the medical and pharmaceutical industries to ensure that Medicare and Medicaid dollars are spent appropriately on safe and effective drugs and devices.

I am following up on my prior letter to you regarding the delayed release of the ENHANCE trial by Schering-Plough and Merck.[1] This study examines whether Vytorin provides better health benefits than generic simvastatin. Vytorin is a pill that combines the statin, simvastatin, with a drug called ezetimibe that decreases absorption of cholesterol by the digestive tract.

It has come to my attention that Schering Plough and Merck would not need to unblind the data to understand that Vytorin performed no better than generic simvastatin. The ENHANCE trial is a non-inferiority study. These studies try to detect a statistically significant difference between treatment groups on the primary endpoint. Once the results are recorded, the study is then unblinded to determine which drug is the better performer. However, if the drugs performed the same, meaning there is no statistically significant difference in the treatments, then this information is apparent before the study has been unblinded.

According to your own press release on the ENHANCE results, "There was no statistically significant difference between treatment groups on the primary endpoint."[2] My

concern is that anyone who had access to the blinded data could have run simulations and learned that Vytorin performed just the same as simvastatin.

My Committee investigators have learned that the ENHANCE trial data were routed from all of the trial centers to Dr. John J.P. Kastelein of the University of the Netherlands. Dr. Kastelein then transmitted the data to the Schering-Plough Research Institute in Kenilworth, New Jersey.

Accordingly, please respond to the following questions and request for documents. For each response, first repeat the enumerated question followed by the appropriate answer.

1. Please explain how the ENHANCE carotid ultrasound data was transferred from the core laboratory to the Schering-Plough Research Institute.

2. Please name all Schering-Plough employees who had access to the ENHANCE data during or after completion of the trial. For each individual, please provide
a. Name;
b. Title;
c. Technical expertise (lawyer, statistician, medical doctor, etc.)

3. Please provide the names of all statisticians at the Schering-Plough Institute. Please indicate which of these employees were involved in any analysis of the ENHANCE trial analysis.

4. Please provide all emails, documents and communications discussing the results of the ENHANCE trial, including any simulations regarding the results. The scope of this request covers employees at the Schering-Plough Institute or elsewhere within the company, from the period of July 2005 to the present.

5. Please provide any and all e-mails and communications between Dr. John Kastelein and Schering-Plough employees from July 2005 until the present.

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

I look forward to hearing from you by no later than February 22, 2008.

Sincerely,

Chuck Grassley
United States Senator
Ranking Member, Committee on Finance

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[1] Alex Berenson, "Cardiologists Question Delay of Data on 2 Drugs," The New York Times, November 21, 2007.
[2] Schering-Plough News Release, "Merck/Schering-Plough Pharmaceuticals Provides Results of ENHANCE Trial," released on company Website on January 14, 2008.

M E M O R A N D U M

TO: Reporters and Editors
FR: Jill Kozeny, 202/224-1308
for U.S. Sen. Chuck Grassley of Iowa
RE: Questions about statements regarding drug trial
DA: Friday, January 25, 2009

Sen. Chuck Grassley made the comment below about the American College of Cardiology clarifying its position today on ezetimibe (Zetia). In an email from CEO Jack Lewin, the College stated, "The benefits of statins have been proven in large studies, while the effect of ezetimibe is unproven." The text of the email appears below Sen. Grassley's quote. The College's January 15 statement is below today's email message, along with a statement made yesterday by Sen. Grassley about the ENHANCE study.

"I'm glad to see that the ACC is putting doctors and patients first. I can only wonder what took them so long. I look forward to their continued cooperation with my investigation," said Sen. Chuck Grassley of Iowa, Ranking Member of the Committee on Finance.

ACC Email on ENHANCE, released on January 25, 2008.
From: Jack Lewin [mailto:jlewin@acc.org]
Sent: Friday, January 25, 2008 10:55 AM
To: Board of Governors
Subject: ACC Response to ENHANCE

Dear BOG:

By now you may have heard through media reports or word-of-mouth that the ACC is receiving inquiries from Congress and others regarding the release of a January 15 public statement regarding the ENHANCE trial. The College's intent in issuing this statement was to advise our physician members looking for guidance in light of the ENHANCE trial data release. A long delay in the release of the data and highly focused media attention led to questions and concerns from our members and their patients. Our statement was designed to minimize undue panic and guide our physicians in communicating with patients about the new data.

The following statement further clarifies our position in light of recent inquiries and news reports:

“The American College of Cardiology (ACC) is concerned that recent news reports and advertisements for ezetimibe (zetia) and ezetimibe/simvastatin (vytorin) could be misinterpreted by patients as an ACC endorsement of ezetimibe for first-line treatment for high LDL (bad cholesterol) or to reduce further risks of coronary heart disease.

The ACC and American Heart Association have published guidelines which recommend that a statin be given as first-line treatment and that alternatives be used only when statins fail to be effective or are associated with significant side effects. The benefits of statins have been proven in large studies, while the effect of ezetimibe is unproven.

Nonetheless, if patients taking medications have questions about their treatment, they should discuss concerns with their physician before making any changes.

The ACC has provided guidance to all our members regarding the recent findings.”

The ACC will of course cooperate fully with all congressional requests for information related to the January 15 statement, including sharing our commitment to patient-centered quality and a high standard of professional ethics.

Thank you for your attention to this important matter.

Jack

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ACC Statement on ENHANCE Trial

January 15, 2008

The ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial results were released by Merck and Schering-Plough Pharmaceuticals on January 14, 2008. The results of the trial show no benefit from the combination of ezetimibe (Zetia) and simvastatin (sold together as Vytorin) over simvastatin alone in terms of affecting the rate of atherosclerosis progression.

The study involved 720 patients with heterozygous familial hypercholesterolemia and showed no significant difference in the primary endpoint between patients treated with ezetimibe and simvastatin versus patients treated with simvastatin alone over a two-year period. The study was designed to prove that Vytorin could slow the growth of plaque in carotid arteries supplying the brain more than simvastatin alone. Media reports indicate that the results of the trial show no benefit from the combination of ezetimibe (Zetia) and simvastatin (sold together as Vytorin) over simvastatin alone.

The American College of Cardiology recommends that major clinical decisions not be made on the basis of the ENHANCE study alone.

According to the American College of Cardiology (ACC), this study deserves serious thought and follow-up. The overall incidence rates of cardiac events were nearly identical between both treatment groups, and both medicines were generally well tolerated. There should no be reason for patients to panic. The difference in IMT changes between the simvastatin group and the Vytorin group was 0.006 mm vs. 0.011 mm.

Health care professionals should speak to their concerned patients using this drug. The ACC is also releasing a public statement explaining that this is not an urgent situation and patients should never stop taking any prescribed medications without first discussing the issue with their health care professional. Further research will be needed in this area to provide conclusive evidence about which lipid lowering strategy is preferred (statin alone vs. statin plus ezetimibe).

Furthermore, the ACC notes that this trial is an imaging study and not a clinical-outcome study. Conclusions should not be made until the three large clinical-outcome trials are presented within the next two to three years. The ACC recommends that Zetia remain a reasonable option for patients who are currently on a high dose statin but have not reached their goal. The ACC also notes that Zetia is a reasonable option for patients who cannot tolerate statins or can only tolerate a low dose statin.

Reports also indicate that the ENHANCE trial has been submitted as an abstract to be presented at the upcoming American College of Cardiology Scientific Session in March, 2008. The late-breaking clinical trial selections by the meeting co-chairs are scheduled to occur in late January.

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M E M O R A N D U M

TO: Reporters and Editors
FR: Jill Kozeny, 202/224-1308
for U.S. Senator Chuck Grassley
RE: Controversy over delayed release of drug trial on Vytorin
DA: Thursday, January 24, 2008

Senator Chuck Grassley, Ranking Member of the Committee on Finance, is asking drug makers Schering-Plough and Merck to explain when the companies first unblinded ENHANCE trial results and to account for sales and payments made for the cholesterol drug Vytorin to Medicaid. Senator Grassley has also written to the Securities and Exchange Commission, the American Heart Association and the American College of Cardiology regarding this matter. Copies of all four letters are posted with this statement at http://finance.senate.gov.

Background information:

Schering-Plough and Merck recently released the results of the ENHANCE trial which studied whether Vytorin performed as well as a generic statin to lower cholesterol levels.

Vytorin is a combination pill of ezetimibe and a generic statin. The ENHANCE trial results found that Vytorin performed just as well as a much cheaper statin. The professional associations issued statements at the time the ENHANCE study was released, so Sen. Grassley is asking for more information about contributions to this statement. For the past three years, Senator Grassley has conducted oversight of various federal agencies and companies to ensure that peer reviewed science forms the basis for decisions in healthcare and healthcare payments.

Senator Grassley's comment:

"In Iowa City, generic simvastatin costs $54.54 for a month's supply while Vytorin costs $112.46. It's fair to assume the public would have benefitted from knowing that a less expensive drug works just as well. Instead, people in Iowa and elsewhere paid more for nearly two years while industry leaders sat on a scientific study that would have revealed this information."